The impact of overactive bladder symptoms on women's sexual activity

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THE IMPACT OF OVERACTIVE BLADDER SYMPTOMS ON WOMEN'S SEXUAL ACTIVITY

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THE DEGREE OF DOCTOR OF PHILOSOPHY

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BSc (Hons), PGCert, RN

Contents

Abstract

The overactive bladder syndrome is a symptom complex incorporating urinary urgency, with or without urgency urinary incontinence and is highly prevalent in women throughout the world. It can have a significant adverse impact on a woman's quality of life both physical and psychological and has been shown to negatively impact on sexual function. The mainstay of treatment has traditionally included conservative therapies such as lifestyle advice and bladder retraining and medication in the form of anticholinergics. Although there is a plethora of data detailing the effect of anticholinergics on lower urinary tract symptoms and general quality of life, scant data are available regarding the impact of anticholinergics on the sexual function of women with overactive bladder syndrome.

This thesis presents an overview of the literature related to the definitions, assessment and management of sexual function and dysfunction in women. It also describes what is known of the impact of lower urinary tract symptoms and specifically overactive bladder on sexual function. Following identification of a knowledge gap, a systematic review questioning "Do anticholinergics improve sexual function in women with overactive bladder syndrome?" was performed and reported.

This led to the development of the research question - 'Does fesoterodine have any effect on the sexual function of women with overactive bladder syndrome?' and this thesis documents the development and initiation of a clinical trial of an investigational medicinal product entitled 'A 12 week, multi-

centre, open label study to evaluate the effect of fesoterodine flexible dosing regimen on the sexual function of women with overactive bladder'.

Although only a fifth of the sample size was recruited, a statistically significant improvement in both the primary and many of the secondary endpoints was achieved indicating an improvement in sexual function. However, due to the lack of a comparison arm it is unclear if this is due to the effect of fesoterodine or a placebo effect. A qualitative analysis of patient goals during the study provided new insights into the impact of overactive bladder on women's quality of life both physically and psychologically.

The clinical trial led to two new research questions -

1. What is the prevalence of sexual activity in women with overactive bladder syndrome attending a London Urogynaecology Outpatient service?

2. How do women want to be approached about the topic of sexual activity and sexual function?

A prevalence survey was conducted which revealed that the levels of sexual activity were lower than expected among the population of women with overactive bladder under study. It raised concerns over the reliability and validity of the questionnaire used and showed that women have a differing views and opinions of what the term 'sexually active' means.

Focus groups were performed and analysed thematically to understand how women want to be approached about sexual activity and sexual function. The key points gained from the groups related to terminology, the desire for

pre-warning regarding discussion about sexual activity and the fact that women's individual preferences need to be identified and considered.

This thesis highlights the inadequacies in current research related to sexual activity and sexual function and overactive bladder and makes recommendations to develop definitions and research methodology to enable future studies in the area.

Acknowledgements

Firstly, I would like to thank Professor Linda Cardozo without whose help and constant encouragement this thesis would not have been possible. During my 12 years in the Urogynaecology department, she has provided me with tremendous support, meticulous supervision and guidance as well as numerous opportunities to travel the world meeting colleagues to share and discuss ideas. She has been an ardent supporter and developer of the advanced nursing role and has offered me opportunities that I would have never dreamed possible. I would also like to thank my second supervisor Mr Cornelius Kelleher for his encouragement to consider different opinions and alternative analyses that have widened my discussions and thought processes. In equal measure I would also like to thank my third 'unofficial' supervisor Dr Angela Grainger, who has been a pillar of information regarding qualitative research and who guided me through a new methodology as the thesis changed over the years.

All research is dependent on teamwork and I would like to thank our extended family at Kings who have given me sage advice and support (particularly Sushma Srikrishna, Dudley Robinson and Ilias Giarenis). I would like to individually thank my nursing team, Rose Orako, Cathy Davis and Marva Thomas for keeping the nurse led service running whilst I have been working on this project. I would also like to thank the two medical students who I teamed up with on this project - Simeon Innocent, my statistician, for all his technical advice and know-how and my second qualitative researcher for chapters 9 and 12, Carlos Curtis. I would also like to thank all the women and clinicians who participated in the research.

Finally, I would like to thank my Fiancé and my family for putting up with me through all the times when I lived and breathed my PhD thesis to the exclusion of everything and everyone else - I am very grateful for your unwavering support and hope that I have made you proud!

List of Abbreviations

AFUD	American Foundation for Urological Diseases
APA	American Psychiatric Association
ARHP	Association of Reproductive Health Professionals
ASEX	Arizona sexual experience questionnaire
BAUS	British Association of Urological Surgeons
BD	Twice daily
BISF-W	Brief index of sexual functioning in women
BMI	Body mass index
BRT	Bladder retraining
BSUGs	British Society of Urogynaecologists
CI	Coital incontinence
CIs	Confidence intervals
CRA	Clinical research associate
CTIMP	Clinical trial of investigational medicinal product
DM	Diabetes mellitus
DO	Detrusor overactivity
DSFI	Derogatis sexual functioning inventory
DSM	Diagnostic and Statistical Manual of Mental Disorders
EAU	European Association of Urology
ED	Erectile dysfunction
ePAQ-PF	Electronic patient assessment questionnaire – pelvic floor
ER	Extended release
FI	Faecal incontinence
FSD	Female sexual dysfunction
FSF	Female sexual function

FSFI	Female sexual function index
GRISS	Golombok Rust inventory of sexual satisfaction
GSTT	Guy's and St Thomas' Hospital
GT	Grounded Theory
HCP	Health care professional
HRQL	Health related quality of life
ICI	International Consultation on Incontinence
ICIQ	International Consultation on Incontinence Questionnaire
ICIQ-fluts-sex	ICIQ female lower urinary tract symptoms questionnaire - sex
ICI-RS	International Consultation on Incontinence – Research Society
ICS	International Continence Society
IIR	Investigator Initiated Research
IR	Immediate release
IMP	Investigational medicinal product
IUGA	International Urogynaecology Association
JCTO	Joint clinical trials office
KCH	King's College Hospital
KCL	King's College London
KHPCTO	King's Health Partners clinical trials office
KHQ	King's Health Questionnaire (also ICIQ-LUTSQol)
LGBT	Lesbian gay bisexual and transgender
LUTD	Lower urinary tract dysfunction
LUTS	Lower urinary tract symptoms
MHRA	Medicine and Healthcare products Regulatory Authority
MMSE	Mini mental state examination
MRI	Magnetic resonance imaging
MSD	Male sexual dysfunction

MUI	Mixed urinary incontinence
MVV	Maximum voided volume
NHS	National Health Service
NICE	National Institute for Health and Care excellence
NSA	Not sexually active
OAB	Overactive bladder
OABQ	Overactive bladder questionnaire
OD	Once daily
OR	Odds ratio
PACQoL	Patient Assessment of Constipation Quality of life
PFMT	Pelvic floor muscle training
PGII	Patient global impression of improvement
PI	Principle investigator
PIC	Patient identification centre
PICO	Population, intervention, comparison, outcome
PISQ	Prolapse and Incontinence sexual questionnaire
PISQ-12	Prolapse and Incontinence sexual questionnaire – short form
PISQ-IR	Prolapse and Incontinence sexual questionnaire – IUGA revised
PK	Pharmacokinetic
PMC	Pontine micturition centre
POP	Pelvic organ prolapse
PPBC	Patient Perception of Bladder Condition
PPIUS	Patient Perception of Intensity of Urgency Score
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
PROMs	Patient reported outcome measures
PTNS	Percutaneous tibial nurse stimulation

PVR	Post void residual
QoL	Quality of Life
RCT	Randomised control trial
REC	Research ethics committee
RPS	Royal Pharmaceutical Society
SA	Sexually active
SAGA	Self-Assessment Goal Achievement questionnaire
SF	Sexual function
SIGN	Scottish Intercollegiate Guidelines network
SMPC	Summary of product characteristics
SNS	Sacral nerve stimulation
SQOL-F	Sexual Quality of Life questionnaire - female
SUI	Stress urinary incontinence
TSQ	Treatment satisfaction questionnaire
TT	Think tank
U	Urgency
UDS	Urodynamics
UI	Urinary incontinence
USI	Urodynamic stress incontinence
UTI	Urinary tract infection
UUI	Urgency urinary incontinence
UK	United Kingdom
UKCS	United Kingdom Continence Society
WHO	World Health Organisation
5-HMT	5-hydroxymethyl tolterodine

Table of Contents

List of tables

Chapter 12

Chapter 13

List of figures

Declaration

The work contained in this thesis was carried out in the department of Urogynaecology at Kings College Hospital, London, between 2010 and 2019, under the supervision of Professor Linda Cardozo.

All the studies were performed by me although I am very grateful for the assistance of my colleagues who helped in recruitment of patients. An external statistician was employed to assist with the analysis of the data.

The studies had full ethics approval and all patients gave written informed consent.

The study was funded by an investigator initiated research grant from Pfizer Ltd.

Angela Rantell

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Publications

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Apostolidis, A., Rantell, A., Anding, R., Kirschner-Hermanns, R. and Cardozo, L., 2017. How does lower urinary tract dysfunction (LUTD) affect sexual function in men and women? ICI-RS 2015—Part 2. NUU, 36(4), pp.869-875.

List of appendices

Grant proposal

Published Articles

Assessment and diagnosis of OAB
Management of OAB
Pharmacological management of OAB
Understanding UI in women
Update on drugs for UI
Assessment of the impact of POP on FSD
Patient goals in OAB
ICI-RS Think Tank–How does LUTD affect SF in men and women? Pt 1 & 2

Clinical trial documents

Fesoterodine Summary of Product Characteristics
Protocol 1.0
Protocol 2.6
Clinical Research File
Patient Information Sheet
Informed Consent Form
GP letter
Study poster
Prolapse and Incontinence Sexual questionnaire - PISQ-12
Sexual Quality of Life Questionnaire Female - SQOL_F
Patient perception of bladder condition – PPBC
King's Health Questionnaire – KHQ
Patient assessment of constipation quality of life questionnaire - PAC-QoL
Self-Assessment Goal Achievement 1st assessment questionnaire – SAGA
SAGA follow up
Research and Ethics Committee approval

MHRA approval
Research and Development approval

Investigations of the screen negative group

Prolapse and Incontinence sexual questionnaire IUGA revised - PISQ-IR
Invite to focus group
Informed Consent Form
Transcript from focus group 1
Transcript from focus group 2

Additional Results

Additional tables from Chapter 7
Regression models from Chapter 8
Full results for Chapter 12

Chapter 1

Introduction / Background to the Study

Introduction

In 2008, the 4th International Consultation on Incontinence (ICI) took place in Paris. At this meeting an international faculty of over 150 health care professionals came together to review current evidence in relation to the assessment, diagnosis and management of all aspects of incontinence. They not only published guidelines in relation to best practice but also made recommendations for future research in line with the gaps that they identified in the knowledge. They recommended that:-

'Urinary incontinence, lower urinary tract symptoms (LUTS) and the treatment of these disorders all have potential effects on the sexual function of women yet little is known about the impact of incontinence treatment on sexual function. It is therefore appropriate that sexual function be considered as one of the domains for investigation in all types of incontinence research.' (Abrams et al 2009)

Professor Cardozo was actively involved as a co-chairman in this meeting and also an editor of the book "Incontinence" published after this consultation detailing their recommendations. At one of the Urogynaecology departmental research meetings following the ICI, Professor Cardozo discussed some of these recommendations for research and highlighted considering how these ideas could be incorporated into the current research strategy within the department.

This thesis will describe the development and implementation of investigations that I have undertaken during the course of study and present the subsequent findings, including those in line with current literature and new discoveries.

The Urogynaecology Department at King's College Hospital

The Urogynaecology Department at King's College Hospital (KCH) NHS Foundation trust was founded by Professor Cardozo in 1979 with a weekly urodynamics session. It is set within a large teaching hospital in south east London that cares for an urban and suburban catchment area and a multi-racial population. It is both a secondary and tertiary referral service, providing expert assessment, diagnosis, conservative, pharmacological and surgical management of LUTS and pelvic floor dysfunction. Figure 1.1 is a picture of the Golden Jubilee Wing at KCH, where the Urogynaecology department is based.

Figure 1.1 Golden Jubilee Wing at King's College Hospital

Today the team comprises four Consultant Urogynaecologists, a sub-specialty trainee, two clinical research fellows, three clinical nurse specialists, three women's health physiotherapists and a health care assistant. Figure 1.2 is a picture of the current team taken at the UK Continence Society (UKCS) Meeting in 2018. The department was accredited by the British Society of Urogynaecology (BSUGs) in 2013 and in 2014, received recognition as a subspecialist provider for complex Urogynaecology from NHS England.

Figure 1.2 The Urogynaecology Team at KCH

The unit receives approximately 1650 new patient referrals per year into our main outpatient clinic and about 1200 patients are seen in our one stop urodynamics clinics per year. On average the department reviews around 250 women per week within the variety of clinical services (outpatient and one stop urodynamic clinics, nurse led clinics, physiotherapy clinics and outpatient, day surgery and in patient surgery lists).

One of the most commonly reported conditions for which women are referred to the service is the overactive bladder syndrome (OAB). OAB is a symptom complex incorporating urinary urgency, with or without urgency incontinence and is highly prevalent in women throughout the world. The condition can have a significant adverse impact on a woman's quality of life (QoL) both physical and psychological and has been shown to negatively impact on sexual function (SF). The mainstay of treatment has traditionally included

conservative therapies such as lifestyle advice and bladder retraining and medication in the form of anticholinergic drugs.

Given that a large proportion of the clinical workload in the unit at KCH involves assessment, diagnosis and treatment of women with OAB and the treatment involves commencing anticholinergic therapy it was decided that in line with the ICI recommendations, I would investigate this group of women further to see what had been studied with regards to anticholinergic therapy and SF.

Literature searching

Having cared for women with OAB for many years, I had a good baseline knowledge of the condition, however, expertise in the field of sexual function was lacking. This study therefore started with a review of the literature associated with female sexual function and dysfunction, including the models of sexual response, prevalence, aetiology, co-morbidities, assessment methods, investigations and treatments available. An overview of my learning from this is presented in chapter 2.

To ensure that I was up to date with my knowledge on the condition in question, a literature review was performed to provide an in depth understanding of the aetiology, prevalence and burden of the disease, as well as a review of the assessment, investigation and current treatment recommendations for OAB. This was followed by a further literature review to understand the impact that OAB can have on SF and a woman's QoL, before finally undertaking a scoping search of the literature to gain an initial understanding of what had been discovered already in relation to anticholinergics and SF. Although there is a plethora of data detailing the effect of anticholinergics on LUTS and general QoL, scant data were available regarding the impact of anticholinergics on the SF of women with OAB. The findings of these enquiries are detailed in Chapter 3.

At that time there were only two clinical trials that had looked specifically at SF with one particular drug (Tolterodine) yet in these trials, SF was not a primary outcome measure. A systematic review critiquing these trials entitled “Do anticholinergics improve sexual function in women with overactive bladder syndrome?” was originally performed in 2011 and updated in 2017 and is presented in Chapter 4.

Following further discussions, it was decided that the whole scope of anticholinergic treatment for OAB was a far too vast an area to investigate and that we should start by focusing on one anticholinergic medication and performing a clinical trial with SF as the primary outcome measure. Fesoterodine was the chosen medication for this study and a review of the evidence related to its use is discussed in chapter 5.

Research Grant Approval

At the time these investigations were being developed, Professor Cardozo was the Principal Investigator (PI) on a national study entitled ‘A 12 Week, Multi-centre, Open Label Study to Evaluate the Efficacy, Tolerability And Safety Of Fesoterodine Flexible Dose Regimen In Patients With Overactive Bladder’. (ClinicalTrials.gov identifier: NCT00806494) (Cardozo et al 2012). It was also known as the SAFINA trial and was sponsored by Pfizer INC. Fesoterodine is the newest of seven anticholinergic agents available on the UK market. At an investigator meeting for this trial the idea of a study looking primarily at SF was discussed with the medical director for the urology division at Pfizer. It was suggested that for health care professionals who would like to investigate a certain action or specific outcomes of one of their medications, an application could be submitted for an Investigator Initiated Research (IIR) Grant which would help fund and supply medication to perform these studies.

A decision was made to apply for one of these IIR grants to perform a study looking at fesoterodine and SF. The grant application (a copy can be found in the appendices) was submitted to Pfizer and after review by their

International Research Department they decided to look favourably on the application and approved the funding and supply of the drug so that the trial could be undertaken. To ensure that I was fully conversant with the drug that would be used during further investigations, Chapter 4 was developed to provide a full review of the investigational medicinal product (IMP) - fesoterodine, including its pharmacodynamics and pharmacokinetic properties, dosing and treatment schedules, efficacy, tolerability and safety.

To gain further insights into pharmacology and the application of drug therapy within Urogynaecology, I also completed a master's level university programme which enabled me to qualify and practice as an independent nurse prescriber.

Clinical Trial of Investigational Medicinal Product

Based on the findings of the literature review and following grant approval, a clinical trial of investigational medicinal product (CTIMP) entitled: A 12 week, multi-centre, open label study to evaluate the effect of fesoterodine flexible dosing regimen on the sexual function of women with overactive bladder was developed and performed. This was a mixed methods study where the effect on sexual function was the primary outcome. Secondary outcomes considered the efficacy and tolerability of the IMP and exploratory studies related to changes in urodynamic parameters. The investigation of patient's goals provided a qualitative investigation of what women wanted to achieve from therapy.

Chapter 6 of this thesis describes the decision making process behind many of the fundamental trial processes including the rationale for the primary and secondary outcome measures employed, the inclusion / exclusion criteria, sampling methods, feasibility and discussions surrounding the ethical considerations of performing this study.

The final trial protocol, approvals process, study initiation and challenges faced in undertaking the study, including problems with recruitment and the

methodology requiring substantial amendments are explained in Chapter 7. Following completion of the study, the plans for the final statistical analysis are also detailed within this chapter.

The presentation of results has been divided into three chapters. Chapter 8 highlights the quantitative results from the CTIMP undertaken. The subject disposition and baseline characteristics are demonstrated along with the statistical analysis from all of the primary and secondary endpoints. Tables and graphical representations are presented to demonstrate changes from baseline to 12 weeks and also include details relating to safety reporting in the study and the longer term follow up at six months.

Chapter 9 discusses and critiques the findings and outcomes of the quantitative investigations comparing results with other relevant literature where available and highlighting new discoveries and hypothesising why these may have occurred. The chapter also outlines the methodological weaknesses and limitations to the study that were identified in the process. Following on from these challenges identified, further research questions arose and additional investigations were performed. The development of these new research questions are also detailed within chapter 9.

Chapter 10 presents the qualitative outcomes of the study and demonstrates the goals women set during the clinical study and the level of goal achievement. A description of the methodology used to analyse the goals is included along with a discussion about the themes that emerged and the relevance of these in the current literature. The goals from the women in this study are also compared to the goals set in a UK wide study to assess for similarities and differences in our clinical population, to understand if we need to adjust our current practice to meet the local populations' needs.

Additional research questions

Following scrutiny of the substantial difficulties recruiting to the trial previously described, further research questions were identified, as illustrated in chapter 9. To try to answer these additional questions further enquiries were developed and performed. Chapter 11 details the methodology and research tools employed to complete these investigations.

Chapter 12 details a prevalence study that was completed within the unit at KCH. The primary aim of this investigation was to assess the prevalence of SA in our OAB population. The secondary aims were to evaluate why women were not sexually active (NSA), to assess if this was bothersome to them, to evaluate variations in SA according to UDS diagnosis and to compare questionnaire responses between the SA and NSA groups. This chapter not only presents the answers to these questions, discussions in relation to these and the impact this may have had on the main trial but also questions the validity of the tool used in the study. It also highlights fundamental issues with terminology that may lead to challenges for all future research in the field of SF.

The second research question identified was related to how women want to be approached about the topic of SF. In a bid to answer this research question and gain insights that may benefit routine clinical practice and future research studies, Chapter 12 details findings from two focus groups for women with LUTS who attended the Urogynaecology outpatients department for assessment and treatment. The aim of these focus groups was to understand how women want to be approached regarding the topic of sexual function along with any barriers they have encountered and what their preferences are regarding when the conversation should be introduced and by whom. The evaluation of these focus groups has led to new insights that can help to develop our clinical practice and potentially help guide recruitment in future studies assessing SF in women with LUTS.

During this time I also took the opportunity to network with other international researchers with an interest in LUTS and SF and co-chaired a "Think Tank" at the International Consultation on Incontinence Research Society (ICI-RS 2015) entitled- How does lower urinary tract dysfunction affect sexual function in men and women? This group not only looked at where the current knowledge gaps are but considered ideal research methodologies to investigate these. Two articles were produced by the group and published in 2017 and these have been included in the appendices.

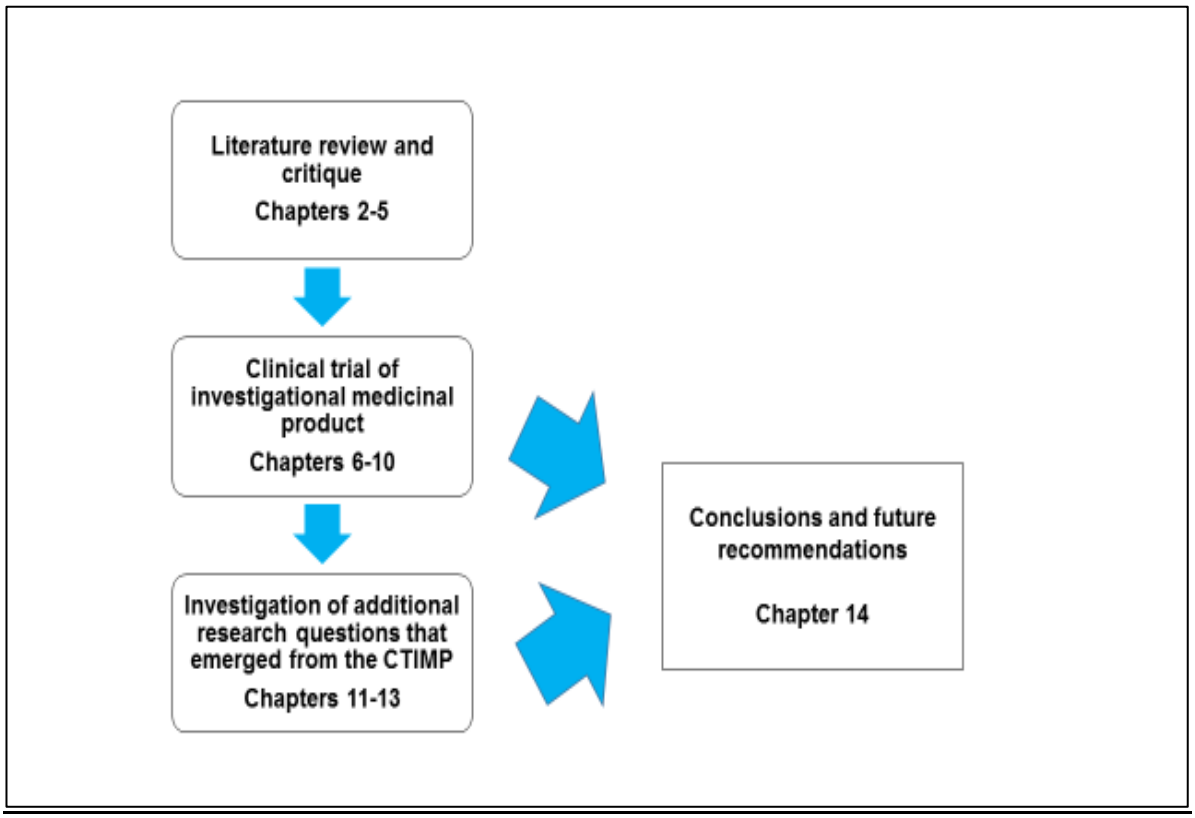
Future recommendations

Based on all the studies undertaken in this thesis, Chapter 14 summarises the conclusions and recommendations that have stemmed from the work presented throughout this thesis. It includes discussions on the fundamental flaws that have been identified in current definitions and the research tools employed. Suggestions for future research have been made based on what has been learnt from this extensive piece of work and the questions that have arisen from the analysis of the data gained during this study.

Finally the Appendices include relevant original papers published as part of this thesis and additional material related to all the investigations undertaken, including the full protocol for the CTIMP and all the questionnaires employed. All patient literature and transcripts from the focus groups have also been included in the interests on transparency.

Figure1.3 demonstrates the flow of investigation throughout the course of this thesis and the chapters relevant to each section of the enquiries.

Diagram 1.3 Trial flow chart.



Conclusions

This thesis documents the work that has been undertaken towards this higher degree. It demonstrates not only the research performed, methodologies utilised and the knowledge gained in the specialist area but also details my development throughout the course of study.

Chapter 2

Female Sexual Function (FSF) and Dysfunction (FSD)

Sexual health is defined by the World Health Organisation (WHO 2006) as the integration of somatic, emotional, intellectual and social aspects in ways that are positively enriching and that will enhance personality, communication and love. According to Masters and Johnson (1966), sexual function (SF) is defined as how the body reacts in different stages of the sexual response cycle. Sexual activity (SA) is the manner in which we express our sexuality. Optimal female sexual health comprises physical, mental, and emotional aspects and there are several variables that influence SF including physiological and psychosocial factors (Tsai et al 2011).

Early research looking at female sexuality was conducted by Kinsey (1953). The sexual practices of American men and women were studied to try to dispel the misconception that women are not interested in sex. It has been suggested that research on female sexuality lags behind research into male sexual function as some cultures have difficulty accepting that female sexual problems are as disruptive to a women's health related quality of life (HRQL) as they are to a man's (Kingsberg and Althof 2009).

As the focus of this thesis is the sexual function of women with overactive bladder syndrome, this chapter aims to provide an overview of the female sexual response, in order to gain an understanding of normal sexual function before considering what female sexual dysfunction (FSD) is, including a review of the literature related to it's prevalence and aetiology. Assessment of sexual function will be described along with a critique of the questionnaires used to measure sexual function / dysfunction and finally a brief overview of treatments for FSD will be discussed.

Models of sexual response

The classic four phase linear model of female sexual response based on a physiological foundation was first introduced by Masters and Johnson (1966). The four phases described are excitement, plateau, orgasm and resolution. Sexual response will vary between different women and for an individual woman on different occasions. Women may not always reach the

orgasmic stage, and the resolution or refractory period is not always observed in women. If they do not experience a refractory period, women cannot respond to additional stimulation. However, in most cases women can respond to repeated stimulation and reach a second or third orgasm soon after the first (Chen C et al 2013).

Similar linear models by Kaplan (1979) and Leif (1977) were also introduced which added desire into the model, however, all these suggested that sexual response is invariant, the same for men and women, and that desire always precedes arousal and is discussed below in more detail. In the brain, a balance of the dopamine-sensitive excitatory center and the serotonin sensitive inhibitory center modulate the desire phase (Basson 2001). The two basic physiological reactions that occur during sexual response are vasoconstriction of the genitalia and increased neuromuscular tension throughout the body (Masters and Johnson 1966). There are, however, a number of other physiological changes that happen to the female body as a result of sexual response and these are described in Figure 2.1 (adapted from Chen C et al 2013).

Figure 2.1 Physiological changes in the female sexual response cycle

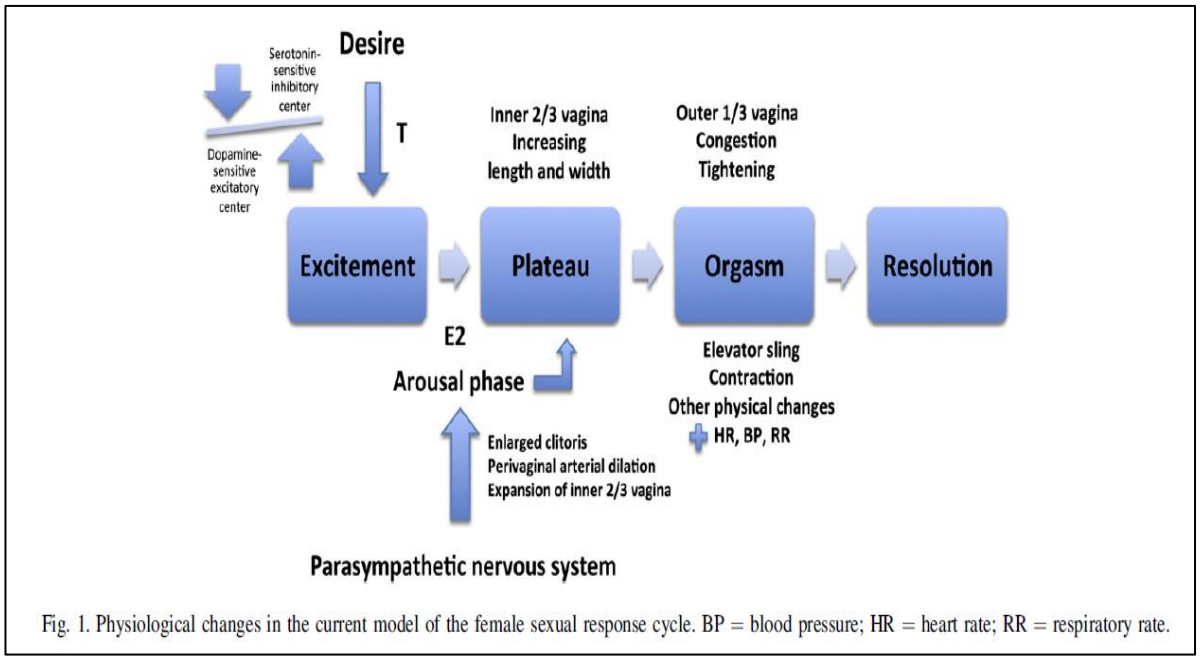


Fig. 1. Physiological changes in the current model of the female sexual response cycle. BP = blood pressure; HR = heart rate; RR = respiratory rate.

These models have been questioned over the years because they presume that men and women have similar sexual responses and do not take into account non biological experiences such as pleasure and satisfaction or place sexuality in the context of a relationship (Whipple 2002, Working Group 2000, Whipple and Brash-McGregor 1997). It is also noted that many women do not move progressively and sequentially through the phases as described. For example they may move from arousal to orgasm and satisfaction without experiencing sexual desire, or may experience desire, arousal and even satisfaction but not orgasm (Whipple 2002)

In 1997, Whipple and Brash-McGregor developed a circular sexual response model to address these issues (See Figure 2.2 from Association of Reproductive Health Professionals (ARHP) 2008). This concept was built on four stages; seduction (encompassing desire), sensations (excitement and plateau), surrender (orgasm) and reflection (resolution). By making the model circular, it demonstrated that pleasant and satisfying sexual experiences may have a reinforcing effect on a woman, leading in to the seduction phase of her next sexual experience.

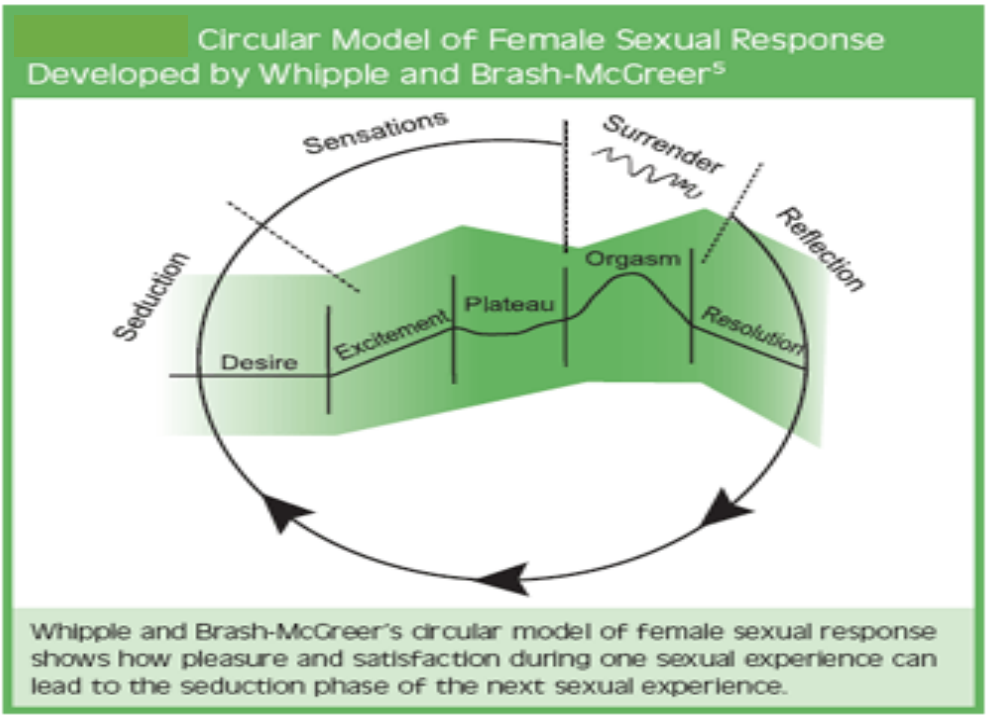


Figure 2.2 Circular Model of Female Sexual Response

Basson (2001) further refined this into a non-linear model of female sexual response that incorporates the importance of emotional intimacy, sexual stimuli and relationship satisfaction, and acknowledges that female functioning is significantly affected by psychosocial issues e.g. satisfaction with the relationship, self-image and previous negative sexual experiences (Figure 2.3 adapted from ARHP 2008). It suggests that women begin a sexual encounter from a point of sexual neutrality and the decision to be sexually active comes from a conscious wish for emotional closeness or as a result of seduction or suggestions from a partner (Kingsberg and Althof 2009).

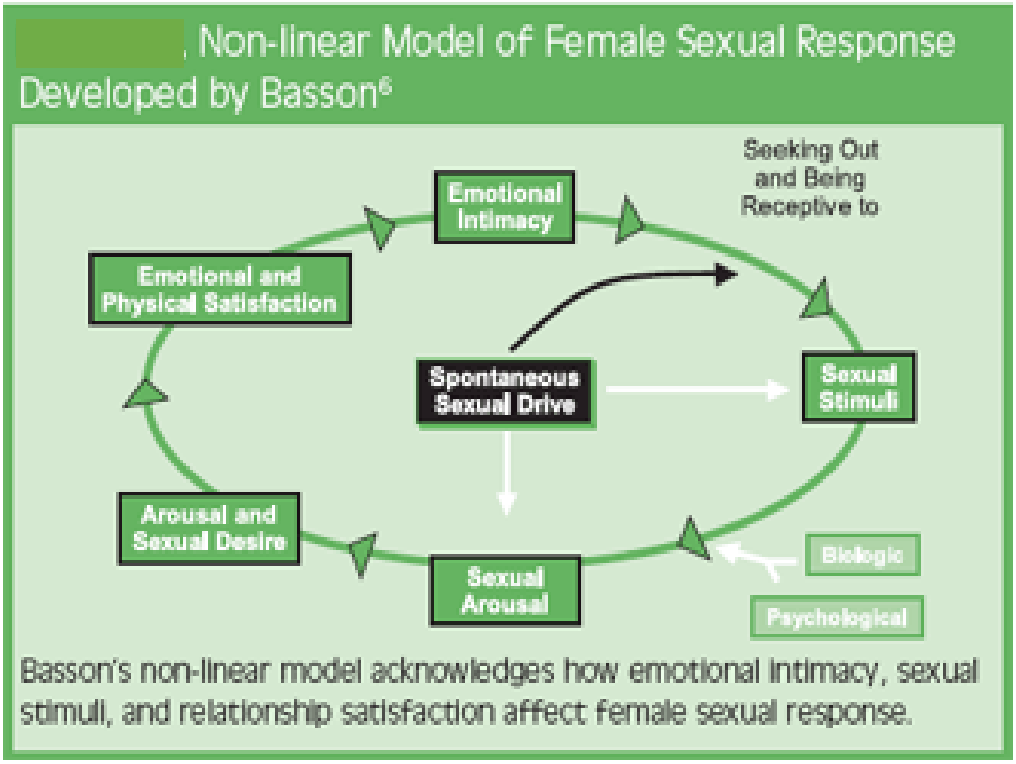


Figure 2.3 Non Linear Model of female sexual response

Studies by Cain et al (2003), Regan and Berscheid (1996) and Galyer et al (1999) have revealed common motivations for women to agree to or initiate sex including a desire to; enjoy the emotional closeness that accompanies and follows sexual activity with a partner, increase their own sense of well-being and self-image, and reduce guilt or anxiety about sexual infrequency. The importance of sex to a woman and man is also a considerable factor in female desire (DeLamater & Sill 2005).

Definitions / Classifications of Female Sexual Dysfunction (FSD)

In the first two versions of the Diagnostic and Statistical Manual of Mental Disorders (DSM) in 1952 and 1968, the concept of FSD did not exist and only the terms frigidity and vaginismus were included in a list of supplementary terms (Graham 2016). As medicine was a very male dominated field at that time it could be suggested that it was not considered important or that women had not felt able to raise their concerns due to societal / gender constraints. At this time, little had changed since the famous Imlach case of the 19th century, where the woman sued a gynaecologist for loss of sexual function after her ovaries were removed and the male dominated jury had to decide if the ovaries were important (Morants-Sanchez 2000). It took a further 20-30 years to break down these barriers for FSD to be defined and classified and many of these new classifications were led by women.

According to the WHO International Classifications of Diseases – 10 (ICD-10), the definition of FSD includes 'the various ways in which an individual is unable to participate in a sexual relationship as she would wish' (WHO 1992). FSD can afflict women of any age, and its expression changes with the endocrinology of advancing years (Buster 2013).

In 1998, The Sexual Function Health Council of the American Foundation for Urological Disease (AFUD) compiled the first consensus based definition and classification system for FSD. They listed five major categories of dysfunction; desire, aversion, arousal, orgasmic and sexual pain disorders (Basson et al 2000a). These are further defined in table 2.1 (Aslan 2008)

Table 2.1 Categories of dysfunction

Sexual disorders	**Definition**
Hypoactive Sexual Desire Disorder	The persistent or recurrent deficiency of sexual fantasies / thoughts and or receptivity to sexual activity that causes personal distress
Sexual Aversion Disorder	The persistent or recurrent phobic aversion to and avoidance of sexual contact with a sexual partner that causes personal distress
Sexual Arousal Disorder	The persistent or recurrent inability to attain or maintain sufficient sexual excitement causing personal distress
Orgasmic Disorder	The persistent or recurrent difficulty, delay in or absence of attaining orgasm after sufficient sexual stimulation and arousal which causes personal distress
Sexual Pain Disorders	Recurrent or persistent genital pain associated with sexual intercourse, including dyspareunia, vaginismus and non coital pain disorders

These classifications, which may coexist, are sub-typed as life-long versus acquired, generalised versus situational and organic versus psychogenic (Basson 2000a). FSD is not always a primary pathology but may be a symptom or a side effect of another. (Basson 2005a). Mouritsen (2009) reported on the 'vicious cycle of FSD and how all areas may be interlinked. (See Figure 2.4)

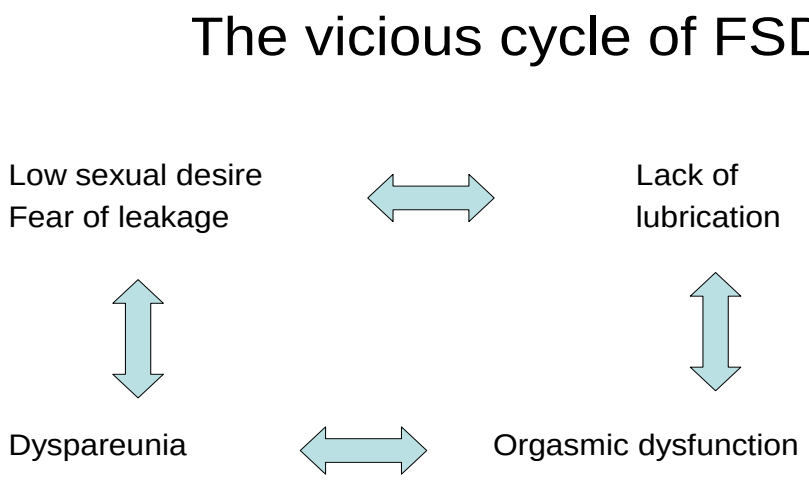


Figure 2.4 The Vicious cycle of FSD.

Following on from this, the DSM-IV defined FSD as ‘disturbances in sexual desire and in the psychophysiological changes that characterise the sexual response cycle and cause marked distress and interpersonal difficulty’ (American Psychiatric Association 2000).

The classification of FSD was further updated in 2004 at the 2nd International Consensus of Sexual Medicine and guidelines were established to aid clinicians to evaluate the clinical significance of symptoms and further define the distress (Basson 2005b).

However, throughout the literature many comments have been made regarding difficulties defining FSD in practice and when a sexual problem should be classified as a sexual dysfunction (Bancroft et al 2003, Chen C et al 2013, Latif 2013). Bancroft and Graham (2011) suggest that the specific challenge is the recognition of the marked variability of women’s sexual experiences and the need to distinguish between transient problems in SF e.g. due to adaptive responses to stressful circumstances and more persistent problems. Over a 10 year period a task force and working group for the American Psychiatric Association (APA) updated diagnostic

categories and criteria for FSD. The DSM-IV was revised and the DSM-V (2013) was adopted. Within this update, the definition of sexual dysfunctions was changed to 'a group of disorders that are typically characterised by a clinically significant disturbance in a person's ability to respond sexually or to experience sexual pleasure' (APA 2013 p423). Their symptoms have to have been present for at least six months and been experienced in 75-100% of sexual encounters. The classification of female sexual desire disorder was removed and female arousal disorder was re-named female interest / arousal disorder to cover a more varied expression of sexual desires in females. Sexual aversion disorder was also removed due to rare use and lack of supporting evidence. Changes to terminology were also introduced and dyspareunia was revised to genital pelvic pain and the classification of vaginismus was replaced with the term penetration disorder (Chen C et al 2013, Derogatis et al 2010). As with all terminology changes, they have been made to either make terms more generalisable (eg. genital pelvic pain), more specific (eg. penetration disorder) or to come in line with new evidence. There are pros and cons to each of these in terms of broadening or narrowing diagnosis for patients, however, this can only make a difference if clinician's are educated about the new terminology and advised about how this may change outcomes for patients or the treatments offered to them. Yet, in current practice in the UK these terms are not well known and not used in routine clinical practice.

Prevalence of FSD

Difficulties estimating the prevalence of FSD in women have been reported and this is thought to be due to the fact that the parameters of FSD are not as clear as those of male sexual dysfunction (MSD) (Laumann et al 1999), and because it is hard to determine the level of distress associated with sexual symptoms in a large-scale survey (Nappi et al 2016). Methods of evaluating FSD and outcomes assessments have varied widely between studies (Hayes et al 2006) and it has been suggested that many place an overemphasis on genital response rather than a subjective assessment of arousal and desire (Graham 2010) or even whether the event was sexually

satisfying despite a limited genital response. Prevalence data suggest that the rates of FSD in clinical populations (ie women attending gynaecology clinics) are between 40-50% (Geiss et al 2003, Nazareth et al 2003, Laumann et al 1999). However, there are very few studies looking at the prevalence of FSD in 'real world' populations, probably due to the difficulties accessing this population and the intimate nature of the subject being investigated. Ventegodt (1998) performed an anonymised assessment of QoL amongst 2460 representative Danish women, which included five SF questions (out of a total of 317 questions). They found that the QoL of individuals with sexual problems was between 1.2%-19.1% lower than the population means (range of population mean QoL 61.5-75.9, range of women with sexual problems mean QoL 57.3-67.5). Lack of sexual desire and lack of a suitable partner were the two most commonly cited sexual problems for women, however, no data were provided relating the sexual problems to age of the respondent, relationship satisfaction, and general health to be able to further comment or justify the reduced QOL.

The Global Study of Sexual Attitudes and Behaviour, included 27,500 women over the age of 40 from 29 countries and considered the prevalence of FSD according to geographical location. It was reported that lack of interest in sex varied from 17% in Europe to 34% in Southeast Asia, lubrication problems ranged from 12% in Europe and the Middle East to 28% in Asia. Pain during intercourse ranged from 5% in Europe to 22% in Southeast Asia and the inability to reach orgasm varied from 10% in Europe to 34% in Southeast Asia (McCabe et al 2016). This study suggests that women in Southeast Asia report the most sexual problems. This could potentially be for a variety of reasons, for example the respondents in these surveys may not have been representative of the population especially given the rural nature of this part of the world or possibly issues with how the questions were translated. Laumann et al (2005) reported early ejaculation and erectile dysfunction to be more prevalent amongst men from Southeast Asia than other parts of the world and that 20% of men in Southeast Asia lacked interest in sex. This may also have a significant impact of the sexual health of the women in the region. It is also important to consider the cultural

and socio-economic aspects that may contribute to these high figures as there is a significant prostitution / sex trafficking issue in that area that may also be impacting upon women's long term sexual function.

Ponholzer (2005) studied the prevalence and risk factors for FSD in a cohort of women undergoing a voluntary health assessment as part of a public health initiative. 703 women between the ages of 20-80 years completed a questionnaire on FSD. 22% reported desire disorders, 35% arousal disorders and 39% orgasmic problems, all of these issues increased significantly with age. 12.9% reported pain disorders but this was more common among the 20-39 age group. However, this study still relied on women volunteering to participate and disclose sensitive information and is unlikely to represent the population.

Wolpe et al (2017) performed a systematic review to assess the prevalence of FSD in Brazil. They reported that the prevalence of FSD ranged from 13.3%-79.3% of the population studied. When considering the specific aspects of FSD they found that sexual desire concerns ranged from 11%-75%, arousal from 8%-68.2%, lubrication from 29.1%-41.4%, orgasm from 18%-55.4% and satisfaction from 3.3%-42%. It was suggested that the range in prevalence occurred due to the differences in the populations studied for example age, marital status, educational level, family income and associated co-morbidities.

Causes of FSD

Gladu (2002) reported four causes of FSD: medical illnesses, psychological illnesses, hormonal deficiencies or the effects of medications. Examples of these causes can be found in table 2.2. Sociocultural and relationship related causes have also been linked with dissatisfaction or discontent with sexual experiences (Tiefer 2002). It is likely that in many cases no one single factor will be the cause but a combination of multiple factors.

Table 2.2 Causes of FSD in women

Medical Illnesses	**Psychological illnesses**	**Hormonal deficiencies**	**Effects of medications**
Hypertension Diabetes Thyroid dysfunction Neurological demyelinating conditions Previous pelvic surgery	Depression Anxiety Bipolar disorders Schizophrenia	Menopausal changes Female androgen deficiency syndrome	Selective serotonin reuptake inhibitors Antidepressants Antihypertensives Tamoxifen Phenothiazines

Buster (2013) developed a table of all the medications associated with FSD which was adapted from the ARHP (2005). It is interesting to note that anticholinergics, commonly used for the treatment of OAB are considered to be associated with arousal disorders but not desire or orgasm disorders. Further discussion of this topic will be included in the next chapter.

The list of medications is demonstrated in table 2.3.

Table 2.3 Medications associated with FSD

Medication	Desire disorder	Arousal disorders	Orgasm disorders
Psychotropics			
Antipsychotics	+		+
Barbiturates	+	+	+
Benzodiazepines	+	+	
Lithium	+	+	+
SSRIs	+	+	+
TCA	+	+	+
MAO inhibitors			+
Trazodone	+		
Venlafaxine	+		
Cardiovascular and antihypertensive medications			
Antilipid medications	+		
Beta blockers	+		
Clonidine	+	+	
Digoxin	+		+
Spironolactone	+		
Methyldopa	+		
Hormonal preparations			
Danazol	+		
GnRH agonists	+		
Hormonal contraceptives	+		
Antiandrogens	+	+	+
Tamoxifen	+	+	
GnRH analogues	+	+	
Ultralight contraceptive pills	+	+	
Other			
Histamine H2 receptor blockers	+		
Indomethacin	+		
Ketoconazole	+		
Phenytoin sodium	+		
Aromatase inhibitors	+	+	
Chemotherapeutic agents	+	+	
Anticholinergics		+	
Antihistamines		+	
Amphetamines and related anorexic drugs			+
Narcotics			+

Note: SSRIs = selective serotonin reuptake inhibitors; TCA = tricyclic antidepressants; MAO = monoamine oxidase inhibitors.

Mouristen (2009) also suggested areas of pathophysiology that can cause FSD (Figure 2.5)

Figure 2.5 Areas of pathophysiology of sexual dysfunction

- Mind and age (neurotransmitters, medication)
- Oestrogens and androgens
- Vaginal epithelium and lubrication
- Vaginal blood flow
- Coital incontinence
- Scar tissue / vaginal dimensions
- Neuropathy
- Pelvic floor muscles

Low oestrogen levels in the vagina, urethra, trigone epithelium and atrophy of the pelvic floor muscles have also been proposed as causes for FSD and lower urinary tract symptoms (LUTS) (Bligic and Beji 2010). Oral contraceptives have been shown to reduce arousal and sexual interest and increase genito-pelvic pain in women (Lee et al 2017).

Several studies have reported increased FSD in women with higher body mass index (BMI) (Assimakopulos et al 2006, Esposito et al 2007, Bond et al 2009). A recent study by Mostofa et al (2017) reported that in young, pre-menopausal population, obese women were more likely to have desire, arousal and lubrication problems compared to overweight women. However, the discussion did not consider whether this was due to hormonal / medical causes or psychological causes eg reduced body image / low self-esteem or functional issues with sexual activity due to body habitus.

Nazarpour et al (2016) performed a systematic review to identify factors affecting SF following menopause. Table 2.4 demonstrates some of the factors identified. Although, this study only assessed women during the menopause, it highlights the complexity of the physical, emotional, social and interpersonal and intrapersonal factors that can all impact upon FSD. These factors represent significant challenges in all research in SF as it is impossible to exclude all the compounding variables.

Table 2.4 Factors affecting SF

Physical Factors	**Psychological / Emotional / Social factors**	**Relationship / Partner Factors**
Age Oestrogen deficiency Type of menopause Chronic medical problems Severity of menopausal symptoms Dystocia history Health status	Depression Anxiety Smoking Alcohol Access to health care Poor understanding of women's health	Partners sex problems Quality of relationship with spouse Partners loyalty Sexual knowledge History of divorce or widowhood Living apart from spouse

Discussing sexual function

According to O'Donnell et al (2005) only 24% of women were not at all embarrassed to discuss sexual problems with a doctor in comparison to 87% when discussing allergies or cold/flu. According to Coyne et al (2007) approximately a third of women would not initiate a discussion about sexual issues with their doctors. In a study of members of the Dutch Urology Association, 40.3% did not think that FSD was routinely relevant to urological practice (Siddall 2010). It has also been suggested that concerns about time restraints, lack of effective treatments and embarrassment may prevent women initiating a discussion about sexual concerns with their doctors (Kingsberg 2006). Rogers et al (2018) report that many women are hesitant to initiate discussions on SF but want their health care professional (HCP) to open the dialogue. It is felt that by asking these questions the HCP is acknowledging and prioritising the role that sexual health plays in overall

wellbeing and this will encourage the woman to openly discuss concerns so that an appropriate assessment can be performed. Further research investigating communication between HCP's and women regarding SF is discussed in chapter 13.

Assessment of sexual problems

Evaluation of FSD can be limited by time constraints, patient / clinician discomfort, difficulty with diagnosis, lack of available services and treatments (Frank et al 2008). In order to perform a full assessment of sexual problems, it is important to create a conducive environment by establishing a rapport and putting patients at ease. It is recommended that a thorough sexual history should include medical, reproductive, surgical, psychiatric, social and sexual information (Hatzichristou et al 2004, Clayton 2003, Berman et al 1999). Many factors, including depression and other psychiatric disorders and medical comorbidities have been identified as confounders in the assessment of SF. (Bancroft 2002). Basson (2000b) published a list of essential questions to include in a sexual assessment (See Figure 2.6), however, the practicalities of asking these questions in a routine gynaecology clinic and the confidence of the clinician performing the assessment may not be conducive to these recommendations. Following history taking a physical examination and or laboratory testing eg hormone profiles or pelvic MRI, and in specialist services or research settings vascular studies, vaginal photoplethysmography, vaginal and clitoral duplex doppler ultrasound and thermal imaging of the genital area may help to rule out underlying pathological factors.

Figure 2.6

Essential questions to include in a sexual assessment

- How does the patient describe the problem?
- How long has the problem been present for?
- Was the onset sudden or gradual?
- Is the problem specific to a situation / partner or is it generalised?
- Were there likely precipitating events (biological or situational)?
- Are there problems in the woman's primary sexual relationship
- Are these current life stressors that might be contributing to the sexual problems?
- Is there guilt, depression or anger that is not being directly acknowledged?
- Are there physical problems such as pain?
- Are there problems in desire, arousal or orgasm?
- Is there a history of physical, emotional or sexual abuse?
- Does the partner have any sexual problems?

It has been reported that the most important factor in the diagnosis of a sexual dysfunction of any subcategory is the presence of personal distress caused by the dysfunction (Latif 2013). More recently guidelines have been developed through expert consensus to establish the minimum elements needed in the assessment of female sexual pain disorders (Goldstein et al 2016). These are demonstrated in table 2.5.

Table 2.5 Pain and psychosocial assessment

Areas	**Specifics**
Pain	Pain quality, time of onset, temporal pattern, duration, location, elicitors, intensity
Musculoskeletal history	Surgeries, injury, fall to the lumbar-pelvic-hip region, coccyx, and sacrum
Bowel and bladder	Habits and function history
Sexuality	Desire, arousal, orgasm, frequency, satisfaction, sexual practice, and distress
Psychological	Thoughts, emotions, behaviours, couple interactions (avoidance, conflict, hypervigilance, partner responses, and self-efficacy) Childhood trauma Current romantic relationship
Comorbidities	Other medical and mental health conditions
Treatment	Previous treatment attempts, interventions, and outcomes
Questionnaires	Standardised self-report questionnaires, such as Female Sexual Function Index

Questionnaires to Assess Sexual Function

Patient reported outcome measures (PROM's) are specifically validated questionnaires that can be used to identify or diagnose a particular dysfunction, assess the severity or impact on HRQL and measure improvement or satisfaction with treatment (Althof & Symonds 2007, Rogers 2013a). They are usually self administered and can be completed by a patient in her own time prior to assessment, encouraging reflection on symptoms and aiding discussion, however, due to the sensitive nature of SF some women may not wish to complete them.

The development of quality of life questionnaires is a complex and lengthy process. It generally involves an initial stage of item generation, which is based on reviews of the literature and subject / expert opinions gained from focus groups / interviews. This is followed by item reduction where subjects and experts express preferences to topics and questions and these views are then translated during an expert meeting to generate a questionnaire. This is then piloted in a small group of subjects prior to more formal testing to confirm content, face, criterion and construct validity and reliability of the measure.

Given this arduous process, there are very few truly high quality questionnaires assessing SF in women. The ICI have performed repeated literature searches over the years as part of the assessment chapter of the textbook to identify questionnaires to assess PROMS. These tools are then subject to a stringent review of the reliability and validity of the measure and the quality of the evidence supporting its development and use in clinical populations. Based on the levels of evidence, the ICI then make recommendations on which tools to use. Gradings are from A+ to C and those with an A+ rating are highly recommended (Abrams et al 2017).

Those available to identify or diagnose a sexual dysfunction include the Brief Index of Sexual Functioning for Women (Taylor et al 1994), the short scale McCoy Female Sexuality Questionnaire (Dennerstein et al 2001), the Female Sexual Function Index (Rosen et al 2000), the Changes in Sexual Functioning Questionnaire (Clayton et al 1997), the Daily Log of Sexual Activities (Leonard et al 2010), the Sexual Interest and Desire Inventory Female (Clayton et al 2010) and the Multidimensional Sexuality Questionnaire (Snell et al 1993).

The Sexual Quality of Life – Female (Symonds et al 2005) is used to assess the impact of FSD on QoL and the Sexual Function Questionnaire (Quirk et al 2002) addresses the consequences of FSD for the woman, her partner and their relationship. Questionnaires regarding SF that are disease specific to women with UI / POP will be reviewed in chapter 3.

Table 2.6 lists all of the questionnaires available to assess sexual function in women and reports the specific aims of each questionnaire as well as the group of patients in which they are validated. It is interesting to note that only one of the questionnaires is designed for couples to complete, not only to assess if the other partner has a sexual problem but also to assess the impact of their partner's problem on them. The questionnaires rating as set by the ICI is also noted. Further critique and the use of these questionnaires will be discussed in Chapter 6.

Table 2.6 Description of questionnaires to assess SF

Questionnaire name	**Number of questions**	**Primary goal of PROM**	**Population Used for validation**	**ICI recommendation**
Brief Index of Sexual Functioning in Women (BISF-W)	22	Self administered questionnaire designed to assess current levels of female sexual functioning and satisfaction	Hetero and homosexual women seeking routine gynaecological care with organic and inorganic causes of FSD	B
McCoy Female Sexuality Questionnaire (MFSQ)	19	Self administered questionnaire to assess aspects of female sexual function	Post menopausal women	C
Female Sexual Function Index (FSFI)	19	Self administered questionnaire assessing key dimensions of sexual function in women	Normal women without any reported sexual problems and women with OAB, SUI and MUI	A
Changes in Sexual Functioning Questionnaire Female (CSFQ – F)	35	A gender specific self reported inventory designed to measure illness and medication related changes in sexual functioning (Based on CSFQ structured interview design).	Medical students and patients with depression	B
Daily log of Sexual Activities	9	Self administered questionnaire designed to provide an outcome measure of the number of sexual events, the number of satisfactory sexual events, and the magnitude of sexual interest or desire	Women with and without HSDD	B
Sexual Interest and Desire Inventory – Female (SIDI-F)	13	Clinician administered tool to quantify the severity of symptoms in women with HSDD and change in HSDD in response to treatment	Women with HSDD	B

Questionnaire name	Number of questions	Primary goal of PROM	Population Used for validation	ICI recommendation
Multidimensional Sexuality Questionnaire	12	Self administered questionnaire designed to measure psychological tendencies associated with sexual relationships	Male and female university students	Not rated
Sexual Quality of Life Questionnaire Female (SQoL-F)	18	Self administered questionnaire to assess the impact of FSD on a women's sexual quality of life and to evaluate the benefits of therapeutic intervention	Women	B
Female Sexual Distress Scale – Revised (FSDS-R)	13	Self administered questionnaire that assess distress associated HSDD and other female sexual dysfunctions	Pre and post menopausal women with and without FSD	B
Derogatis Sexual Functioning Inventory (DSFI)	25	A self reported version of semi structured interviews designed to provide a multidimensional assessment of sexual function in men and women	Community samples of men and women – no validation in women with FSD	A
Golombuck Rust Inventory of Sexual Satisfaction (GRISS)	56	A self administered questionnaire to evaluate both the quality of a heterosexual relationship and each partner's level of sexual functioning within that relationship	Heterosexual couples from general population, gynae clinics and sex therapy groups	A

Table 2.6 cont. Description of questionnaires to assess SF

Treatment of FSD

Many different treatments have been suggested for FSD, however, these depend on the type of dysfunction experienced and many other factors independent to the individual. Table 2.7 was developed based on the reviews by Clayton & Juarez (2017) and Tsai (2011) to consider many of the medical, physical and psychosocial treatments available to women with FSD.

It is considered that most women will need a multimodal treatment package that initially includes education on health promotion and management of comorbidities, some form of psychological therapy and physical therapy and if the conservative measures are ineffective then pharmacological treatment is prescribed.

Considering pharmacological treatments, testosterone has been shown to improve components of FSD including sexual desire, arousal, pleasure and overall satisfaction (Khera 2015). Systemic oestrogen therapy alone is insufficient to cure symptoms of FSD (Lobo et al 2003). However, topical oestrogen therapy is commonly used for dyspareunia (Rioux et al 2000). Many of the pharmacological treatments noted are used ‘off license’, only Flibanserin and Ospemifene are licensed for the treatment of FSD.

Psychological therapies are often the most difficult to access in routine clinical practice and onward referral to specialist services with sex therapists / psychosexual counsellors is preferable but in the UK very few of these services exist.

Table 2.7 Treatments for FSD

Psychosocial Treatments	**Medical treatments**	**Physical therapies**
Psycho-education Sensate focus Cognitive restructuring Communication training Self and/or partner exploration Sexual fantasy training Directed masturbation Mindfullness	Optimising treatments for comorbidities Oestrogen Testosterone PDE5 inhibitors (Phosphodiesterase type 5) eg Sildenafil Selective Oestrogen receptor modulator (SERM) eg Tibolone / Ospemifene Norepinephrine – dopamine disinhibitor eg Flibanserin Dopaminergic agonists Prostaglandins Herbal therapies eg ginkgo biloba extract	Modifications of lifestyle Eliminating risk factors eg smoking, illicit drug use, obesity Pelvic floor Exercises Trigger point therapy Vaginal dilator therapy Eros Clitoral device Vibrator therapy Acupunture Lubricants

<u>Conclusions</u>

SF is a complex process that includes physical, social and emotional factors. FSD appears to be a prevalent condition in clinical populations, however, the true prevalence in the general population is still not known. It can however, have a significant impact on a woman's QoL and relationships. The challenges in assessing the prevalence of FSD in the general population include language variations, cultural differences and access to all populations. As there are so many variables it may only be possible to

research certain groups of women individually. Given that research into this field has only started to develop over the past 40 years it could also be considered that the definitions are still dominated by a 'male' model of sexual functioning rather than fully recognising the underlying psychological and emotional factors that are essential to a woman's SF.

A full sexual and medical history is an essential element to understand and categorise FSD and appropriate validated questionnaires should be used to aid this process. Treatment is not only multimodal but also multidisciplinary, ensuring that both the physical and psychological health of women is addressed.

The literature searching and writing of this chapter helped me to develop an understanding of sexual function and dysfunction in women including possible causes, confounding variables and available treatments. This knowledge has help with counselling women in the clinical setting who report sexual problems. It has also provided the general knowledge base needed to be able to further investigate SF and FSD in a more specific clinical population. Chapter 3 will describe the clinical population under investigation in this thesis and review the evidence related to the conditions impact on SF.

The elements of sexual assessment and review of the tools / questionnaires to support an assessment of SF not only provided the theoretical basis to develop my clinical skills in this area, but also helped to guide the development of the clinical trial and trial procedures discussed in Chapter 6.

Chapter 3

Overactive Bladder Syndrome and its Impact on Sexual Function

Introduction

According to Haylen et al (2010), overactive bladder (OAB) is the term used to describe the symptom complex of urinary urgency with or without urgency urinary incontinence, usually with frequency and nocturia, in the absence of urinary tract infection or other obvious pathology. It is estimated to affect 17% of the adult female population in North America and Europe (Milson et al 2001, Stewart et al 2003).

In this thesis, the population of women under investigation are those with OAB. This chapter aims to provide an overview of the definitions, prevalence and aetiology of OAB. It will discuss how OAB is diagnosed and consider current treatment recommendations. Following on from this it will then consider the impact of OAB on women's sexual function, reviewing the available literature and current assessment along with the impact it has not only on partners but on QoL. It will finally consider the impact that treatment of OAB may have on a woman's SF.

Definitions

The definition of OAB reported above was established following a consensus report by IUGA and ICS as the most recent standardisation document defining terminology for Female Pelvic Floor Dysfunction. In the report, urinary urgency was defined as a complaint of a sudden, compelling desire to pass urine which is difficult to defer. Urgency urinary incontinence is the complaint of involuntary loss of urine associated with urgency. Frequency is the complaint that micturition occurs more frequently during waking hours than previously deemed normal by the woman and nocturia was set as the complaint of interruption of sleep one or more times because of the need to pass urine when each void is preceded and followed by sleep. OAB can be broken down into two subcategories, OAB dry and OAB wet. The latter group experience urgency urinary incontinence whereas the former do not experience incontinence. Coyne et al (2012) have suggested that women with OAB symptoms can distinguish between normal urge (or desire) and

“urgency” suggesting that urinary urgency is a continuum rather than an all-or-none phenomenon.
Other relevant definitions that may be discussed later include Urinary Incontinence (UI) defined as the complaint of involuntary loss of urine and Stress Urinary Incontinence (SUI) defined as the complaint of involuntary loss of urine upon effort or exertion eg coughing, sneezing.

Prevalence

There is an inherent difficulty in trying to define the prevalence of OAB worldwide, based on the current literature. This is because definitions have changed twice over the last 16 years, so a lot of the older studies are no longer comparable. There are issues with terminology, as the term of urgency does not apply in all languages so it is difficult to assess if they are all measuring the same thing. Also, more recently it has been suggested that prevalence studies reporting lower figures than earlier work is due to the fact that bothersomeness is now taken into account and although many women may experience symptoms, they do not all find then bothersome or consider then to be a problem.

In 2001, Milsom et al conducted a population based survey across Europe in which 16,776 interviews were performed. They reported that the overall prevalence of OAB in individuals 40 years and above was 16.6% and increased with age. They also found that frequency was the most commonly reported symptom (85%) whilst 54% complained of urgency and 36% UUI. However, in that study, OAB was defined here as the presence of chronic frequency, urgency and UUI (either alone or in any combination), which means these figures may not be accurate in line with current definitions.

In 2006, Irwin et al performed a further population based survey (EPIC study) of LUTS among subjects in Canada, Germany, Italy, Sweden and the United Kingdom (UK) and reported on 19,165 men and women over the age of 18 years. 11.8 % complained of symptoms suggestive of OAB (defined as urgency, with or without UUI) and 64.3% reported at least one urinary

symptom. In addition, OAB was found to be more prevalent than all types of UI combined (9.4%). The prevalence of OAB is known to increase with age and Irwin et al (2011) predicted that in view of the aging population, by 2018, 546 million individuals worldwide would be affected.

A recent study by Chuang et al (2017), was performed to determine the prevalence of OAB in individual's ≥ 40 years in China, Taiwan and South Korea. It was reported that 1 in 5 individuals were affected by OAB with an overall prevalence slightly higher at 22.1% in women compared to men. However, in prevalence studies in Japan it is reported as 11.8% overall and only 10.1% in women, compared to 15.3% in men (Funada et al 2017). This study also considered factors that influence OAB and found that environmental factors including age, depression and the consumption of cake to be more positively associated with OAB than genetic variants.

A longitudinal population based survey by Wennberg et al (2009) assessed the prevalence of LUTS in a group of women in 1991 and again in the same group of women in 2007. They found that although the overall prevalence of OAB symptoms was similar, the OAB wet group had increased from 15% in 1991 to 28% in 2007 and the OAB dry group decreased. In addition, the prevalence of urgency increased from 17% to 26% and nocturia increased from 38% to 58%. This study supports the findings of the Milsom (2001), showing that the incidence of OAB symptoms increases with age. It was also suggested that the natural progression of symptoms would account for the increase in incontinence as well as the increase in age of the patients. However, there was no evidence available regarding whether the women had received any treatment for their urinary symptoms and the impact this may have upon the findings. Heidler et al (2011) also studied the natural history of OAB in women and suggested that OAB is a dynamic disease with long-lasting stable disease courses as well as remissions and progressions. However, this could be associated with the time of year the survey was performed, whether they were receiving treatment and were adherent to therapy at the time, or related to other co-morbidities.

OAB is a chronic long-term condition and in a study of 174 women, 88% had persisting OAB symptoms lasting >10 years (Garnett et al 2009). Reeves et al (2006) suggested that due to the aging population the prevalence of OAB will rise by 24% over the next 20 years. Bladder symptoms and sensations of urgency are highly variable in the general population however a study by Stewart et al (2010) found that the longer duration of time with urinary symptoms predicts more persistent symptoms.

Anatomy and Aetiology

The lower urinary tract is controlled by both the central and peripheral nervous systems in addition to local regulatory factors (Andersson 1993). This is demonstrated in Figure 3.1. Contraction of the detrusor smooth muscle and relaxation of the internal urethral sphincter result from activation of parasympathetic neurons located in the sacral parasympathetic nucleus at the level of S2 – S4 (De Groat et al 1981, Shah & Leach 2001). The axons pass through the pelvic nerve and synapse with postganglionic nerves in either the pelvic plexus, the ganglia on the surface of the bladder (vesical ganglia) or within the walls of the bladder and urethra (intramural ganglia) (Lincoln & Burnstock 1993).

The sympathetic innervation of the bladder and urethra arises mostly from the thoraco-lumbar region T10 – L2 of the spinal cord. The axons travel mainly in the hypogastric nerve but also pass through the paravertabral chain and enter the pelvic nerve. The predominant effects of the sympathetic innervation of the lower urinary tract are inhibition of the parasympathetic pathways at spinal and ganglion levels thus causing relaxation of the detrusor muscle and contraction of the internal urethral sphincter.

Bladder sensation is transmitted via several different neuronal connections. Proprioception is relayed by the mechanosensitive, myelinated alpha delta (Aδ) fibres and long latency unmyelinated C fibres in parasympathetic afferents travelling in the pelvic nerve to sacral segments S2 – S4. The Aδ

fibres respond to passive distension and active contraction, therefore conveying information regarding bladder filling (Janig & Morrisson 1986). C-fibres have a high mechanical threshold and respond mainly to chemical irritation of the bladder urothelium or cold (Habler et al 1990). Abnormal sensation may be produced by differing systemic medical conditions including diabetes mellitus (DM) and neurological diseases of the central nervous system.

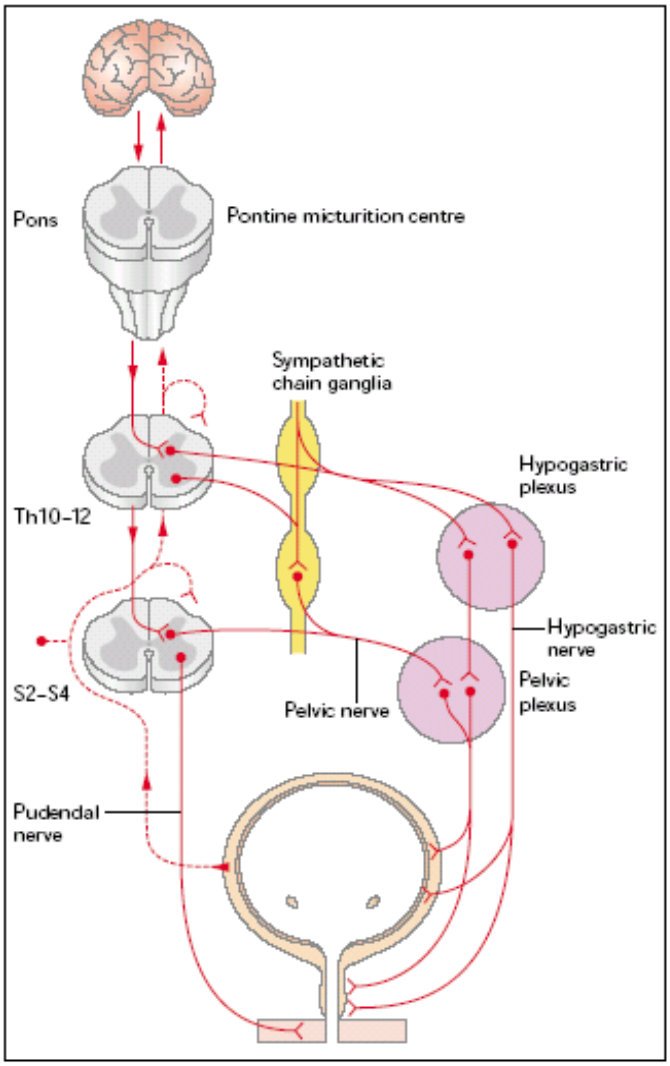


Figure 3.1 Innervation of the lower urinary tract. The bladder and urethra receive parasympathetic and sympathetic as well as somatic innervation. Sensory afferents can be found in the pelvic hypogastric and pudendal nerves. (Adapted from Andersson 1993)

Normal adult bladder function is characterised by inactivity of the parasympathetic efferent pathways and absence of involuntary bladder contractions during the filling (storage) phase. In addition, the pressure in the bladder remains low during filling because of the compliance of the bladder wall until capacity is reached. This is largely achieved by the arrangement of detrusor muscle fibres, reflex inhibitory pathways and the absence of connective tissue restriction. A disturbance in any of these factors may result in increases in intravesical pressure at a lower capacity and the bladder may become hypertonic due to poor compliance. A significant increase in intravesical pressure may lead to incontinence, particularly if the urethral sphincter is compromised, whereby the threshold at which the intravesical pressure exceeds the urethral closure pressure is reduced.

The bladder physiologically fills at a rate of 0.5 – 5 ml/min until it reaches its capacity (Monga & Sultan 2003). The maximum capacity of the bladder is determined by the vesico-elastic properties of the bladder, the physical limits of smooth muscle strength and the resistance of the outflow tract. However, in normal women the maximum capacity is rarely reached since voiding is prompted when the bladder has filled to functional capacity. This is generally between 400mls – 600mls (Cardozo et al 1993) and depends upon bladder sensation, activity, compliance and voluntary voiding patterns.

Micturition is not completely understood although several key events are known to occur, these are co-ordinated by the pontine micturition centre (PMC) in the brain stem. The PMC receives information from afferent neurones in the bladder and also from the cerebral cortex and hypothalamus. It also has a role in controlling the descending pathways of the micturition reflex. At a socially acceptable and convenient time, following central initiation and then activation of the sacral parasympathetic nucleus, there is a co-ordinated release of acetylcholine from the parasympathetic post ganglionic nerve terminals in the bladder (De Groat et al 1993). Following this there is a depolarisation of smooth muscle cells with an inward flow of calcium ions. Actin/myosin activation leads to a sustained contraction of detrusor smooth muscle fibres which provide the power to micturate and

empty the bladder. The urethra normally opens during the first phase of the voiding cycle but it is unclear if this is an active or passive phenomenon secondary to an increase in intra-vesical pressure. In some women gravity alone may lead to the expulsion of urine with the subject simply having to relax the external urethral sphincter and pelvic floor.

The symptoms of OAB are thought to primarily be due to involuntary contractions of the detrusor muscle during the filling phase of the micturition cycle. These involuntary contractions, when observed during urodynamic studies (UDS), are termed detrusor overactivity (DO) and are mediated by acetylcholine-induced stimulation of bladder muscarinic receptors (Anderson 1997). Previous studies have reported that approximately 44% of women with OAB symptoms have DO on UDS (Hashim & Abrams 2006).

Acetylcholine is a neurotransmitter released from parasympathetic nerves. Bladder contraction occurs when acetylcholine binds to muscarininc receptors on the detrusor muscle. There are five types of muscarinic receptor, but only M1, M2 and M3 have been identified in the lower urinary tract (Rigby 2003). These receptors can be found in other tissues including the salivary glands, the heart, intestines and respiratory system. Noradrenaline is released by the sympathetic nervous system and when it binds with adrenergic receptors it causes the detrusor muscle to relax and the internal urethral sphincter to contract.

Anticholinergics are the most commonly used pharmacological treatment for OAB. They are usually muscarinic receptor antagonists and are thought to suppress bladder afferent activity by blocking muscarinic receptors in the urothelium, myofibroblasts and detrusor, thereby reducing intravesical pressure and involuntary detrusor contractions and improving overactive bladder symptoms. However, the fact that the muscarinic receptors are commonly found in other tissues accounts for the significant side effects associated with current treatment of OAB.

The true aetiology of OAB continues to be a widely debated topic and many different theories have been proposed within the studies reviewed. Harrison (1987) suggested that bladder outflow obstruction may lead to OAB through cholinergic denervation of the detrusor and subsequent super-sensitivity to acetylcholine Chu & Dmochowski (2006) report that ischemia may injure nerves and lead to smooth muscle damage and impaired contractility. Myogenic dysfunction secondary to altered structure or disordered function of the detrusor smooth muscle (Brading 1997) and bladder inflammation resulting in increased neuroplasticity in sensory nerves (Dupont et al 2001) have also been considered as a cause for OAB, yet the true aetiology of OAB is still poorly understood and may be subject to many confounding factors such as genetics, poor toilet training and bad habits, and psychosomatic factors eg anxiety.

Physical Burden of OAB

Coyne et al (2004) performed a study to evaluate the burden of OAB, specifically urinary urgency and frequency on Health Related Quality of Life (HRQL). This was part of the National Overactive Bladder Evaluation Program (NOBLE). 919 participants completed HRQL questionnaires. They found that the experience of urinary urgency has a significant negative effect on HRQL and increases symptom bother, more so than incontinence, frequency or nocturia in this sample.

Women with OAB report an increased prevalence of depression, skin infections, vulvo-vaginitis, falls and fractures and UTI compared to age matched controls. (Darkow et al 2005)

Psychological burden of OAB

The symptoms associated with OAB have been reported as detrimental to psychological well-being (Toozs-Hobson 2010). Nicholson et al (2008) described specific emotions experienced by individuals with OAB including embarrassment, low self-esteem and self-blame.

The EpiLUTS study was a cross sectional population-representative survey performed in the USA, Sweden and the UK. It was designed to evaluate the impact of LUTS on urinary specific HRQL. They reported that both men and women with LUTS had the lowest levels of HRQL (compared to those without LUTS) and 53% of women with LUTS meet the self-reported screening criteria for clinical anxiety (Coyne et al 2009a) and associated depression (Coyne et al 2011). The negative impact of OAB on family members has also been demonstrated (Coyne et al 2009b).

Kinsey et al (2016) performed a systematic review of the psychological impact of OAB. Their review of 32 papers found that people with OAB had greater levels of depression, anxiety and embarrassment / shame. In comparison to people without OAB they also reported difficulties with social life, impact on sleep and sexual relationships and a lower QoL. Generally people with OAB wet reported a greater impact than those with OAB dry.

It is interesting to note that a study by Pretorius et al (2014) suggested that even if medication is effective in alleviating symptoms of OAB and the physical burden they impose, it may not improve the psychological effects associated with OAB. This was further investigated by Kinsey et al (2017) who found that even when OAB symptoms had improved, patients did not feel better and found it difficult to let go of worries and fears around OAB. The need for ongoing support even after successful treatment of symptoms was recommended.

The link between anxiety and OAB has been considered in previous studies and is being investigated further. Currently, researchers are considering that there might be an association between an anxious temperament and OAB syndrome reflecting serotonergic dysfunction (Saribacak et al 2014)

Economic burden of OAB

Prevalence data from the EPIC study have also been used to investigate the economic impact of OAB (Irwin et al 2009). The estimated total direct cost of OAB for the UK is just over €1 billion per year. These costs include prescriptions, pad provision, diagnostics, medical consultations and management of medical sequelae such as clinical depression, UTIs, skin infections and fractures. This total cost did not include admission and care provided in nursing homes for patients with OAB wet which was estimated at €579 million.

Tang et al (2014) reported that patients with OAB and UI have a significantly higher health resource utilisation, lower HRQL and reduced productivity compared to adults with OAB without incontinence. A population based cross sectional internet survey has been reported involving 2876 men and 2820 women in the US looking at the impact of OAB on work productivity (Sexton 2009). Overall those men and women complaining of OAB wet reported the lowest levels of work productivity and the highest levels of daily work interference. Wu et al (2005) determined that employees with OAB have an average of 2.2 more days per year of medical absenteeism. The total cost of absenteeism associated with OAB has been estimated at €233 million per year in the UK (Irwin et al 2009).

The cost implications associated with OAB increase as the treatments become more invasive, therefore all patients should start with simple measures and therapy should only graduate in invasiveness as necessary (Sanford 2014).

Help seeking behaviour

OAB is a distressing problem that can lead to depression and social isolation (Bradway et al 2008). However, OAB remains underreported as many sufferers are still reluctant to discuss their condition with their health care provider (HCP) or their family despite increased awareness and improved

diagnosis and treatment (Abrams et al 2000). There is also a misconception that urinary symptoms are an inevitable outcome of advancing age (Keller 1999). The Wennberg study (2009) showed that only 6-7% of participants sought help from the healthcare system for their UI. Benner et al (2009) found that although 45.7% of patients with the symptoms of OAB had discussed these with their HCP, only 8.1% were currently receiving treatment for their symptoms, despite 22.5% being prescribed medication for their symptoms in the last year. This is likely to be related to women's perception of what is bothersome to them.

O'Donnell et al (2005) performed a study to assess the proportion of women who consult their doctor about UI and explored factors associated with help seeking behaviour in France, Germany, Spain and the UK. Overall, only 31% of women had consulted a doctor but women in France and Germany were more likely to seek help than those in Spain and the UK. The reasons for these differences are unclear but may be related to culture, or the health systems available and access to health care. Although in the UK a National Health Service (NHS) is available to all, challenges in getting appointments in primary care and the potential for having to disclose personal information to GP receptionists in order to get an appointment may prevent embarrassed patients from seeking help. They also noted that women who reported using pads were significantly more likely to consult a doctor. Willingness to stay on a prescription medication and women who had spoken to others about UI, were the two most predictive factors for help seeking behaviour. Older age, UI subtype and bother have also been shown to be predictors of care seeking in women with UI (Minassian et al 2012).

It has been suggested that reluctance to seek help or mention urinary symptoms during clinical consultations may be due to the patient's belief that the symptoms are not severe enough to warrant review, or the misconception that they are an unavoidable outcome of aging or child bearing and do not represent a valid medical condition (Dmochowski & Newman 2007). Filipetto et al (2014) reported that on average the length of time from symptom onset and seeking help for urinary symptoms was

3.5years, and patients expressed a preference for clinicians to initiate the conversation about symptoms.

A systematic review of the impact on QoL of OAB concluded that at variance with other chronic conditions, QoL deterioration in OAB patients is characterised by its hidden and embarrassing nature. This suggests that clinicians need to raise awareness of the impact that these symptoms can have, help patients to improve their self-confidence to report symptoms, as well as, encouraging sufferers to have treatment for their condition to overcome its hidden nature (Bartoli et al 2010).

Assessment and Diagnosis of OAB

During the course of this thesis and working in clinical practice an exploration of the assessment and diagnosis of OAB was undertaken with a particular focus on National and International recommendations and guidelines. An article providing an overview of best practice in the assessment of women with LUTS and making a diagnosis of OAB was written and published in the Nursing Standard journal in 2013 and is included in the appendix.

Initial assessment should include a full medical history (including gynaecological, obstetric, surgical and neurological history, abdominal and vaginal examinations, rectal examination (if indicated to rule out faecal loading), completion of a three day bladder diary, urinalysis and measurement of post void residual urine. The impact that these symptoms have on QoL and desire for treatment should also be assessed. There are many condition specific questionnaires that can be used in the screening and assessment of LUTS, the impact that they have on QoL and overall bother. The most commonly used questionnaire to assess the symptoms impact of LUTS is the Kings Health Questionnaire also known as the ICIQ-LUTSqol (Kelleher et al 1997). There are also more condition specific questionnaires such as the International Consultation on Incontinence Overactive bladder questionnaire also known as the ICIQ-OAB, which was designed to evaluate both continent and incontinence symptoms of OAB, their impact on QoL and

the outcome of treatment. Further discussion on questionnaires will be included in Chapter 6.

Management of OAB

There is a raft of clinical guidelines available e.g. NICE CG171 (2013), ICI (Abrams et al 2017), EAU (Lucas et al 2012) that all make practice recommendations for the management of OAB. The general consensus is that conservative management of OAB, including bladder retraining (BRT), lifestyle advice, weight loss, pelvic floor muscle training (PFMT), review of concurrent medications and adjustment of other modifiable risk factors e.g. constipation, smoking and environment should be first line therapy for all women. In the UK it is usually considered that this stage of management should take place in primary care.

BRT involves a programme of patient education and a scheduled voiding regimen. The goals of bladder retraining are to normalise urinary frequency, improve control over urinary urgency, increase bladder capacity, decrease incontinence episodes, prolong inter-voiding intervals and improve the patient's confidence in bladder control. This is achieved through teaching patients urge-suppression techniques, such as distraction, curling toes or perineal pressure (Wyman et al 2009). There are many different methods of urge suppression and strategies that can be adopted. These methods when combined with delayed voiding aim to ultimately expand the voiding interval and bladder capacity. The mechanism by which BRT works is not clear, however it is thought to improve central control of the bladder. But, its success takes time and is highly dependent on the motivation of the patient and enthusiasm of the health care professional. There is currently no consensus on the optimal regimen.

The next stage is pharmacological management and this traditionally starts with the prescription of anticholinergic agents (also known as antimuscarinics) and these will be discussed in more detail later in this chapter. It may also include the use of the Beta 3 agonist, tricyclic

antidepressants, synthetic vasopressin analogue and topical vaginal oestrogens for post-menopausal women. Women often try several different types or combinations of medications during the course of their treatment. If pharmacological treatment is unsuccessful they will then go to third line therapies which are more invasive and costly such as intra-detrusor injections of onabotulinum toxin A, neuromodulation (either sacral or percutaneous) or surgical augmentation of the bladder e.g. clam cystoplasty or ileal conduit diversion. For women who are unsuitable for, or do not wish to have major surgery, insertion of a suprapubic catheter may be considered or some women may choose to just manage containment with absorbent products and pads.

Role of UDS

Referral into secondary care services for women with OAB is usually considered for those who have failed conservative therapy and have tried at least one anticholinergic without significant benefit. At this point, more invasive diagnostic investigations may be performed such as subtracted cystometry (also known as urodynamic studies (UDS)).

Cystometry is the method by which the pressure/volume relationship of the bladder is assessed during filling and voiding. It involves the simultaneous measurement of intravesical and intra-abdominal pressures. Electronic subtraction of the intra- abdominal pressure from the intravesical pressure enables the detrusor pressure to be calculated and compared with changes in bladder volume and flow rate. Cystometry aims to characterise detrusor and urethral function during the filling and voiding phases. This is demonstrated in Table 3.1 (Rantell 2016).

Table 3.1 Urethral and detrusor function during cystometry.

Phases of cycle	Urethra	Detrusor
Filling	Should remain closed and competent but can: • be incompetent due to physical stress, but without an associated rise in detrusor pressure (stress incontinence) • be incompetent as a direct result of an involuntary rise in detrusor pressure (detrusor overactivity)	Should remain relaxed/stable throughout filling but can: • show abnormal involuntary contractions (detrusor overactivity) • show a gradual rise in pressure with filling (low compliance)
Voiding	Should be appropriately relaxed but can: • be constricted, leading to outflow obstruction (obstructed cause)	Should contract efficiently under voluntary instruction but can: • be under-active or acontractile (possible neuropathic cause) • show high-pressure contractors (if over-active or needing to overcome an outflow obstruction)

The presence of involuntary detrusor contractions during filling or on provocation that the patient cannot suppress is diagnostic of detrusor overactivity. These may or may not be associated with symptoms of urgency. If there is a gradual rise in detrusor pressure during filling to >15 cmH2O, but without phasic contractions, this is termed ‘low compliance’. This can be artefactual owing to superphysiological or fast bladder filling. If there is a neurological condition present, such as multiple sclerosis, this is often accompanied by marked low compliance. If leakage occurs on coughing, with an associated rise in intra-abdominal pressure, but in the absence of abnormal detrusor activity, urodynamic stress incontinence is diagnosed.

Questions have been raised over the years regarding the role of UDS in women with OAB given that less than half of women will be found to have DO and successful responses to nonsurgical and surgical interventions for OAB do not absolutely correlate with a finding of pre-intervention DO on UDS (Nitti et al 2010a, Malone Lee et al 2009, South 2007). This links to the potential other causes of OAB symptoms. Lee et al (2010) reported that patients with OAB have increased bladder sensitivity and Finney et al (2006) suggest a sensory disorder is the principal cause of OAB symptoms in some individuals as they found that, at clinically relevant doses, antimuscarinics have little effect on bladder contractility. It could therefore be suggested that these agents primarily act on sensory variables such as urgency, time to first sensation to void, and urinary frequency.

However, it is considered a need to rule out those women with idiopathic OAB from those with other underlying pathology that may be adding to or complicating symptoms eg voiding dysfunction or mixed urinary incontinence (MUI) or where there is suspicion that there is risk to the upper tracts eg due to decreased compliance. Failed or unsatisfactory response to empirical pharmacological therapy is also considered an appropriate indication for performing UDS in women (Abrams et al 2018, Rovner & Goudelocke 2010).

It is also important to consider the difference in those women who are found to have DO on UDS. The presence of DO has been shown to have a more negative impact on the quality of life of women compared to those with OAB symptoms (Giarenis et al 2013) and this information may change how women are counselled in real life practice and what treatments they are offered.

In the researcher's place of work, women are referred following failed conservative or medical therapy in primary care. In line with the above indications, UDS in these women forms part of their routine assessment.

Effectiveness of anticholinergics

A systematic review was performed by Herbison et al (2003) to determine the effectiveness of anticholinergic drugs for the treatment of OAB. It reported that although there were statistically significant differences between anticholinergic drugs and placebo, the effect was small and may be of questionable clinical significance. However, a report by Hartmann et al (2009) reviewed the evidence regarding treatment of OAB, UUI and related symptoms and found that even though treatment effects were quite modest, HRQL and treatment satisfaction measures imply that such improvements are important to women. Jonas (2007) suggested that what matters to patients when seeking treatment for OAB goes beyond the mere presence of symptoms, and the bother and discomfort the symptoms cause are more important in their personal assessment of condition severity and hence the satisfaction with and perceived value of treatment.

A study by Herschorn et al (2014) considered whether patient characteristics could predict the responsiveness to treatment of OAB with antimuscarinics. They reported that shorter duration of OAB symptoms, younger age, female gender and lack of previous antimuscarinic pharmacotherapy are all factors that predict a greater change in outcomes and the response to treatment. It has also been suggested that the ability to predict who will respond to therapy may help to guide treatment decisions e.g. who will need to take prescribed medication, who will need to be titrated to higher doses of medication. This may help to optimise outcomes through individualisation of pharmacotherapy. Ultimately, treatment is usually multimodal and far more complex than the prescription of medicines, however, understanding the wishes of patients will help guide treatment choices and thus their efficacy.

Adherence and persistence

Adherence to anticholinergic medication has always been a concern and in a review of patients taking anticholinergics, 12 months after therapy was initiated, the persistence rate was 14-35% (lower with generic and higher

with branded medication) depending on the drug treatment (Wagg et al 2012). A systematic review of persistence and adherence to anticholinergic therapy was conducted in 2011 (Sexton et al). They found that in 12 week clinical trials, rates of discontinuation ranged from 4-31% and in every day clinical practice from 43-83% within the first 30 days of treatment with rates rising over time. It was reported that over half of patients never refill their initial prescription and the most common reason was concern about the balance between the efficacy and tolerability of the anticholinergic agents. Sears et al (2010) designed a study to see if patients who do not pay for medication were more likely to adhere to therapy. However, still 35% of patients did not refill a prescription for anticholinergic medication. The most common reasons for discontinuation with treatment are dissatisfaction / lack of efficacy to control symptoms (Benner et al 2009, Campbell et al 2008, Basra 2008).

A recent study by Tran et al (2016) reported that the persistence is better when the patient's care is under subspecialist supervision rather than a general community setting. Although specialist education on OAB has not been shown to improve persistence (Sung et al 2015, Schneider et al 2014).

Over the years the lack of persistence with treatment has been a focus for drug development, with treatment moving from immediate release preparations requiring multiple daily doses to modified / extended release preparations allowing single daily dosing. Alternative routes of administration have been developed eg transdermal patch, topical gel, and an intravaginal ring to try to avoid the adverse effects associated with first pass metabolism. New classes of drugs (eg a beta 3 agonist) have been developed to try to improve efficacy and tolerability of treatment. However, in the real world studies, persistence with treatment remains low.

There is a lack of evidence relating to the duration of treatment with anticholinergics and it could be considered that patients believe that they are only having 'a course' of treatment and then discontinue treatment. Lee et al (2011) reported that discontinuation of anticholinergics resulted in higher

symptom relapse and retreatment rates regardless of treatment duration. It has been suggested by Nazir et al (2015) that branded drugs may be more cost effective in the treatment for OAB than low cost generic treatment due to better efficacy and tolerability which in turn improves symptom control and persistence. This could be because of supportive patient programmes provided with some of the branded products.

Despite all these concerns with efficacy and tolerability a report from the ICI (Andersson et al 2017) states that anticholinergics remain the first line pharmacological treatment for OAB.

Impact of LUTS / UI on SF

Although LUTS have been shown to affect many aspects of women's QoL, one aspect that is often overlooked is the impact that it has on a woman's sexual function. The importance of HCP's assessing both urinary and sexual health concerns during patient encounters is emphasised by Chen J et al (2013). Sutherst and Brown (1980) stated that 43% of women attending an incontinence clinic felt that their urinary symptoms were adversely affecting their sexual lives. Pauls et al (2006) reported that up to 64% of sexually active (SA) women attending a urogynaecology clinic suffer from FSD.

To enable measurement of SF and LUTS, researchers have focused on developing questionnaires to measure the impact of symptoms. Quality of life questionnaires have not only been developed to assess SF function in women (as discussed in chapter 2), but disease specific questionnaires to assess SF in women with LUTS / UI have also been developed and are discussed in more detail later in this chapter.

There are significant variations in prevalence figures seen however, this is often because of the populations being assessed, the definitions being used, the evaluation method used or the fact that in many studies all women with any form of UI are grouped together and they do not differentiate for each

subtype of incontinence. Aslan et al (2005) designed a study to evaluate the impact of UI on SF and recruited 21 incontinent women (3 with SUI, 9 with OAB and 9 with MUI) and 18 healthy controls. SF was assessed using the Female Sexual Function Index (FSFI) which is a validated and reliable questionnaire assessing desire, arousal, lubrication, orgasm, satisfaction and pain. All domain scores were significantly lower in incontinent women with the exception of pain. However, they did not demonstrate any differences between the different types of incontinence but the number of women in this study is too small to draw conclusions.

In 2015, Su et al explored the association between UI and SF in a non-clinical population. They found that all types of UI showed a significant association with FSD with an odds ratio of 1.6-1.8. When breaking down the outcomes to individual symptoms, UUI was a risk factor for decreased sexual lubrication and increased pain, while MUI was associated with reduced sexual satisfaction. A recent case control study in Brazil performed by Felippe et al (2017) evaluated sexuality in continent and incontinence women. Incontinent women presented a higher prevalence of sexual abstinence than their counterparts (53% vs 29.2%). Women with UI also have less sexual desire, foreplay, harmony with partner, sexual comfort and satisfaction. These associations are correlated so that the greater the severity of UI the worse the impact on SF.

Age and postmenopausal status have been shown to be associated with increasing severity of UI and compromised SF (Zohre 2014). In 2011, Ghannam et al measured the impact of UI on sexual dysfunction in older Americans. Of 3000 adults aged between 57-85 years, 46% reported UI. Incontinent women were 1.89 times more likely to have anorgasmia and 2.4 times more likely to lack sexual interest compared to continent women.

Many studies assessing LUTS and SF have specifically looked at those who report some form of urinary incontinence during sexual activity. Munaganuru et al (2017) performed a study to evaluate the prevalence and impact of UI during sex and 25% reported experiencing coital incontinence (CI). 19% of

the women reported being subjectively bothered by this and 16% restricted SA for fear of UI. According to a systematic review by Pastor (2013) the prevalence of CI ranges from 0.2%-66%.

Shaw (2002) undertook a systematic review of the literature to assess the prevalence of sexual impairment in women with UI and the prevalence of urinary leakage during sexual activity from publications between 1980 - 2001. Prevalence of CI in clinical settings ranged from 10-56% and impairment in SF was reported as 0.6-64%. However, there are significant challenges in comparing data due to differing definitions, and methods of assessment. The review suggested recommendations for standard definitions and measures of CI and sexual impairment to establish reliable prevalence estimates. Most recently Grey et al (2018) assessed the self-reported prevalence of CI in a large cohort (2312 women) in a Urogynaecology setting using the ePAQ-PF. The overall prevalence of CI was reported as 21%, 24% reported CI at orgasm and 15% reported CI at penetration. It was also found that symptoms of OAB and SUI were independently associated with both types of CI.

It is only recently in 2018 that ICS / IUGA have published a joint report on the terminology for the assessment of sexual health of women with pelvic floor dysfunction (Rogers et al 2018). Within this report, Coital urinary incontinence (CUI) (previously only written as CI) is defined as UI occurring during or after vaginal intercourse. However, it goes further to define specific times of UI and introduces the terms of orgasmic urinary incontinence (UI at orgasm)(previously known as climacturia), penetration UI (UI at penetration including penile, manual or sexual device) and for those with OAB dry, coital urinary urgency (CUU) which is defined as the felling of urgency to void during vaginal intercourse. A final new term of post coital LUS symptoms – such as worsened urinary frequency or urgency, dysuria, suprapubic tenderness has also been added. However, it may take several years from now for clinical trials to adopt this new terminology and report findings in line with this and it will still not be comparable with previous studies.

It is also important to acknowledge that there may be other types of fluids that women may expel during sexual activities. Female ejaculation (FE) is the secretion of a few millilitres of a thick, milky fluid by the female prostate (Skene's glands) during orgasm. Squirting (SQ) is defined as the orgasmic transurethral expulsion of tenths of millilitres of a form of urine containing various concentrations of urea, creatinine and uric acid (Pastor & Chmel (2018). However, this thesis will not address these phenomena which are poorly understood and still contentious within the published literature.

OAB and SF

Intercourse and orgasm have been reported as triggers for OAB symptoms and are associated with significant distress (Zilberlicht 2018). There have been many studies that show the negative impact of OAB on SF (Salonia et al 2004, Milson et al 2009, Coyne 2008a, Chen J et al 2003, Kim et al 2005, Sand et al 2006, Sen et al 2007, Walters et al 1990, Sen et al 2006, Cohen et al 2008, Hansen 2004, Dmochowski & Newman 2007, Pace et al 2011, Nilsson et al 2011). Heidler et al (2010) found that one in four patients with OAB wet reported a negative impact on their sex life. One of the largest prevalence studies performed was by Coyne et al (2011) as part of the EpiLUTS study. Its aim was to describe sexual health outcomes in men and women with continent and incontinent OAB compared to those with no or minimal urinary symptoms, and to evaluate correlates of decreased SA and enjoyment. 8,085 women completed the survey and all women with OAB experienced worse sexual health compared to those with no symptoms. Those with OAB who were incontinent were significantly more likely to report diminished SA and enjoyment with sex. They also reported that women with OAB wet are less likely to be SA than OAB dry women and women without OAB.

A smaller prevalence study was completed by Heidler et al (2010) as part of a health screening project in Vienna. 17.7% of respondents reported symptoms of OAB and 38.1% complained of OAB wet. 28% of those with

OAB felt that it had a negative effect on their sexual lives and in women with OAB wet this effect was more significant than in those with OAB dry.

Oh et al (2008) also evaluated the impact of SUI and OAB on HRQL and SF in Korean women and concluded that although both have a detrimental impact on HRQL, women with SUI experienced more pain during intercourse and CI. A study by Schimpf et al (2009) reported that women with UUI and MUI have lower HRQL score that those that are continent or only report SUI. The study by Coksuer et al (2011) and Karbage et al (2016) corroborate these findings.

Juliato et al (2017) evaluated women with OAB to correlate the severity of their urinary symptoms with their SF. They found that women reporting greater symptom severity (according to the ICIQ-OAB score) have worse SF, in the arousal, lubrication, orgasm and pain domains of the FSFI. Chuang (2017) also reported that increased symptoms severity of OAB is associated with a poorer sexual QoL.

Controversies in the diagnosis of FSD in women with UI

At the start of this project when the protocol was developed and the initial literature search was performed a variety of studies demonstrated the prevalence and impact of FSD in women with pelvic floor disorders. However, with the update of the DMS-V in 2013, not only was the terminology and classification changed but new criteria for the diagnosis of FSD were added (Graham 2016). Female sexual dysfunction now includes the following criterion: 'the sexual dysfunction is not better explained by a nonsexual mental disorder or as a consequence of severe relationship distress or other significant stressors and it is not attributable to the effects of a substance / medication or another medical condition' (APA 2013 p424). Given this criterion sexual disturbances associated with incontinence or any other pelvic floor disorder should not be classified as a sexual dysfunction, even if they cause personal suffering and distress (Mota 2016).

For many women, sexual difficulties may be multifactorial and the presence of urinary symptoms may not be bothersome or impact on their sexual functioning so it raises the question of how to differentiate which factors impact the most on sexual functioning, in order to define a dysfunction or disorder?

Questionnaires to assess the impact of LUTS on SF

Chapter 2 discussed the PROMs used to assess SF in women. This section will specifically examine those PROMs identified by the ICI (Abrams et al 2017) that have been validated to assess the impact of UI / POP on SF in women

The PISQ-12 assesses sexual function after surgery in women with UI and POP (Rogers et al 2003). The Prolapse and Incontinence Sexual Questionnaire – IUGA revised (PISQ-IR) (Rogers et al 2013b) was developed to assess the impact of pelvic problems on sexual desire, frequency, satisfaction, orgasm and discomfort (Abrams et al 2017). The Sexual Function Questionnaire (SFQ) is the only questionnaire specifically designed to assess SF in women with OAB. Table 3.2 presents all the identified questionnaires by the ICI to assess SF in women with LUTS, reporting their primary goal and their ICI rating. These will be discussed further in Chapter 6 when justifying the questionnaires used in the main study in this thesis.

Table 3.2 Condition specific questionnaires to assess the impact of LUTS on SF

Questionnaire name	**Number of questions**	**Primary goal of PROM**	**Population Used for validation**	**ICI recommendation**
International Consultation on Incontinence questionnaire – Vaginal symptoms ICIQ-VS	14	Self administered questionnaire to assess the effects of vaginal symptoms and associated sexual matter on sexual quality of life for sexually active females	Women	A
International Consultation on Incontinence Questionnaire – female Lower Urinary Tract Symptoms Sex (ICIQ-FLUTSsex)	4	Self administered questionnaire to assess sexual matters associated with urinary symptoms and related bother		A
Pelvic Organ Prolapse / Urinary Incontinence Sexual Questionnaire (PISQ)	31	To assess sexual function after surgery in women with pelvic floor dysfunction	Women with pelvic floor dysfunction	B
Pelvic Organ Prolapse / Urinary Incontinence Sexual Questionnaire short form (PISQ-12)	12	To assess sexual function in women with incontinence and prolapse	Women with pelvic floor dysfunction	B

Questionnaire name	Number of questions	Primary goal of PROM	Population Used for validation	ICI recommendation
Pelvic Organ Prolapse / Urinary Incontinence Sexual Questionnaire IUGA revised (PISQ-IR)	19	Self administered questionnaire assessing key dimensions of sexual function including bother in women who are sexually active and those who do not report sexual activity		C
Sexual Function Questionnaire	31	Self administered questionnaire used to assess the impact of OAB on sexual health / function in the male and female population	Men and women with with OAB	C

Table 3.2 (Cont.) Condition specific questionnaires to assess the impact of LUTS on SF

Urodynamic diagnosis and SF

In order to understand the pathophysiological mechanisms of incontinence during orgasm, Serati et al (2008) recruited women with incontinence during intercourse and divided them into two groups: women with CUI at orgasm or at penetration. These forms of CUI were then correlated with the urodynamic finding of DO. Of the 49 women who reported incontinence at orgasm, 69.4% had DO compared to only 28.9% of the 83 women who leaked on penetration. They concluded that in the majority of cases of incontinence at orgasm is associated with DO.

Khan et al (1988) had previously tried to understand the mechanism of incontinence during orgasm and UDS studies demonstrated simultaneous bladder contractions and urethral relaxation. This theory is supported by the work of El-Azab et al (2011) and Moran et al (1999) who report that CUI is almost invariably a symptom of SUI with urethral sphincter incompetence. According to Lua et al (2017) a maximal urethral closure pressure < 30 cmH2O was associated with CUI again demonstrating that urethral function plays a vital role in maintaining continence during coitus

Hilton (1988) performed cystometry to establish the prevalence of UI occurring during intercourse and to define the UDS diagnosis of sufferers. Of 400 consecutive women questioned, 324 were SA and 24% experienced incontinence during intercourse (two thirds on penetration and one third on orgasm). For the group who leaked on penetration 70% were shown to have urodynamic stress incontinence (USI) and 4% DO. However, for the group who experienced incontinence at orgasm, 42% had USI and 35% were found to have DO.

Cohen et al (2008) reported that women with DO and UI have significantly worse SF than women with normal urodynamics. Yip et al (2003) showed that marital relationships and sexual function were negatively affected in women who had USI or DO. In a report that studied the relation between different types of incontinence and sexual health, Urwitz-Lane (2006) showed that among SA women with UI, SF as assessed by the PISQ-12 does not differ according to type of incontinence. These papers suggest many different reasons for this effect including embarrassment, fear of CUI on penetration and orgasm, loss of confidence, fear of smelling, loss of libido.

Madhu et al (2015) reviewed data from a UDS clinic with a total of 11,689 women over a 10 year period. They reported that the prevalence of CUI was 11.8% of women with LUTS undergoing UDS. The majority of the women described mixed symptoms and CUI was associated with USI (OR=2.35) and DO (OR=1.22) but not DO incontinence. Associated risk factors included parity, obesity, smoking and antidepressant drug usage.

Further work by Serati et al (2011) has tried to measure bladder wall thickness in women with CUI to consider if this could predict DO. They found that women with DO and CUI at orgasm had significantly greater bladder wall thickness values and that CUI at orgasm could be a marker of a more severe form of DO.

A study by Gordon et al (1999), prospectively evaluated the relationship between sexual dysfunction and UDS diagnoses in 100 consecutive women. SF was assessed with a detailed questionnaire that calculated a total sexual function score (TSF). They found that women with DO had lower TSF scores than those with SUI and MUI.

Although all of these studies have performed UDS in women who report specific symptoms. None of them have performed the cystometry whilst they are having intercourse or during orgasm or during masturbation to confirm the UDS

mechanism at the time of penetration or orgasm, or to assess UDS parameters associated with coital urinary urgency. This is likely due to the significant artefact that would be produced on the UDS trace as symptoms were reproduced and the potential for errors in pressure measurement related to vaginal intercourse and repeated thrusting let alone the issues related to privacy, dignity, consent and ethical approval as this would need to be in a research setting.

Psychological Impact of OAB on SF

There have been several qualitative studies assessing the psychological impact of OAB on SF. Coyne et al (2007) led six focus groups for women with OAB (three continent and three incontinent). Half of the incontinent women cited OAB, aging and the menopause as the reason for their reduction in sexual desire. The majority of the incontinent women were embarrassed by their incontinence resulting in a loss of self-image. Embarrassment is also associated with loss of urine during intercourse, malodour, and the need to dispose of pads before intercourse (Clark & Romm 1993). All women with OAB complained of difficulty achieving orgasm. The causative factors cited included fear of incontinence, pain and anxiety related to intercourse.

Coyne et al (2007) found that OAB often put strain on relationships because of loss of intimacy, body image concerns and fears of incontinence. They also reported less SA due to leakage and interruptions during sex (Coyne et al 2009a) and have significantly more worry about their future sexual life than healthy controls (Coyne et al 2011) . Low body image was also cited as a reason for having less sex in the study by Nicolson et al (2008). Roos et al (2014) also found that body image plays a key role in the SF of women with POP and UI and has the biggest impact on willingness to engage in SA.

Qualitative research involving interviews with Turkish women to identify the feelings and experience of the effect of UI on SF reported themes such as shame, blame and guilt, fear that UI symptoms could occur during intercourse, individual coping mechanisms such as going to the toilet frequently before SA, avoiding SA were considered and many women did not discuss their concerns with their partners. The overriding theme was that embarrassment had led to an inability to enjoy SA (Akyuz et al 2014).

The impact of women's coping methods when trying to self-manage CUI including urinating prior to sexual intercourse, deferring intercourse, interrupting intercourse prematurely, avoiding certain positions, hurrying through sex and avoiding orgasm may also significantly strain relationships and prevent the woman from relaxing and enjoying sex.

Pelvic organ prolapse, UI and SF

POP is often cited as associated with symptoms of OAB. However, when reviewing the evidence of the impact of POP and OAB on SF most studies again do not differentiate and just report figures for UI as a whole. Rogers et al (2001) compared SF in women with and without UI and/or pelvic organ prolapse (POP) using a validated condition-Specific questionnaire, the Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire (PISQ), and concluded that PISQ scores were significantly lower among women with UI/POP than in those without ($P = 0.003$). Women with UI/POP have poorer SF, as measured by the PISQ, and report less frequent SA. In addition, women with UI/POP are more likely to restrict SA for fear of incontinence. Women with POP and UI are more likely to report decreased libido, decreased sexual excitement, and difficulty achieving orgasm during intercourse when compared to women with UI alone (Ozel et al 2006, Handa et al 2004). This is potentially as the prolapse 'gets in the way' and obstructs intercourse.

Barber et al (2002) suggested that POP is more likely than UI to result in sexual inactivity and be perceived as affecting sexual relations. Jha and Gopinath (2016) confirmed this and reported that patient and partner avoidance of SA was greater in women with POP than those with UI. A literature review by Yount (2013) on the impact of pelvic floor disorders and pelvic surgery on women's sexual satisfaction and function conveyed a warning, that although surgical procedures can alleviate symptoms they cannot guarantee optimal sexual satisfaction, SF or cure of the disorder.

It has been suggested that evaluation of the effects of SUI and other LUTS on SF is often biased by their common association with other pelvic floor disorders including POP which also affects sexual satisfaction (Fatton et al 2014). In clinical practice it is very common for women to have concomitant UI and POP. In the main trial described in this thesis, women with significant POP were excluded. To fully understand the effect of POP (and treatment of POP) on SF in this group of women a review of the literature was performed and an article entitled 'Assessment of the impact of urogenital prolapse on sexual dysfunction' was published in Maturitas in 2016. This is included in the appendix.

Impact on partners

Bekker et al (2010), identified that several studies had revealed that UI impairs women's sexual functioning and satisfaction, however there was no knowledge about the effects of UI on the functioning of their male partners. They asked the women attending an outpatient appointment for urological assessment and their partners to complete the Golombok Rust Inventory of Sexual Satisfaction questionnaire (GRISS). Of the 189 couples who completed the questionnaires 42.9% of the women reported UI. The women with UI demonstrated lower overall SF, lower frequency of intercourse, were more likely to show avoidance behaviour and have more problems with communication. Men with partners with UI also reported an overall diminished SF, lower frequency of intercourse,

reduced satisfaction and were more likely to have erectile problems. However, there were no questions as to whose problems started first.

Face to face interviews were performed by Beji et al (2005) with 32 incontinent women who reported urinary leakage during intercourse and 60 asymptomatic controls. When compared to the control group, incontinent women were 4.7 times less satisfied with their sexual lives and their partners had ejaculation without full erection 3.1 more times (which may have added to the decreased satisfaction). During these interviews several methods of coping with leakage during intercourse were volunteered and these are shown in table 3.3 below.

Table 3.3 Methods of coping adopted by women with leakage problems during intercourse.

Ways of coping with problems	**N**	**%**
Micturating prior to sexual intercourse	6	18.8
Keeping the partner unaware of the problem	16	50
Deferring intercourse	9	28.1
Partner suggests anal coitus	2	6.3
Ignoring the problem	8	25
Interrupting intercourse prematurely	6	18.8

Cassells and Watt (2003) examined the carer's perspective on the effect of incontinence on sexuality and found that although UI did not affect sexual intimacy, it did affect sexual intercourse and sleeping in separate bedrooms was common. Faecal incontinence was found to have a far greater effect on SF than UI.

It has also been reported that significantly more women with OAB had previously been sexually abused than women with SUI or a control group (Jundt et al 2007)

Impact of treatment for OAB on SF – Antimuscarinics

Successful treatment with first, second and third line therapies (conservative therapies, medical therapy and invasive therapies eg SNS) have been shown to improve female SF scores (Moore 2016). However, there is still sparse evidence to evaluate the benefits to SF with drug management of incontinence (Mota 2016). It has been suggested that medical therapy for OAB may reduce the fear of urgency and/or leakage during SA (Wehbe 2010). If women are to have fewer anxieties surrounding their bladder, this may improve desire and may also help them to relax which may reduce pain and improve orgasm. However, antimuscarinics are associated with side effects including dry mouth, and it could be considered that this could negatively affect a woman's ability to kiss as well or perform oral sex. Given the 'drying effect' that they have on the body it could also be considered that there might be an adverse effect on lubrication and therefore increase pain during intercourse, all of which would negatively affect SF.

Sand et al (2006) analysed the sexual domain of the KHQ in a group of 2878 patients receiving transdermal oxybutynin for their OAB symptoms over a six month period. They showed a reduction in CI from 22.8% to 19.3%, partner relationships improved in 19.6% but worsened in 11.9% and the effects of OAB on their sex lives improved in 19.1% but again worsened in 11.2% of patients. However, although 87% of this patient cohort were women, the paper does not separate out the groups in the analysis so these results may be biased. In a further paper by Sand et al (2009) there was a recommendation for future research into the effect of treating OAB symptoms with fesoterodine on sexual

function and quality of life in women. A full systematic review of the literature related to this is presented in chapter 4.

Impact of treatment for OAB on SF – other treatment modalities

A small prospective controlled study by Zachariou et al (2018) examined the effect of mirabegron on female sexual function. The demonstrated statistically significant changes in the total score and each domain score of the FSFI following three months of treatment compared to the control group.

For MS patients receiving onabotulinum toxin A, regaining continence following treatment was associated with a statistically significant improvement on total FSFI scores however, remaining wet left impact unchanged (Giannatoni et al 2015). This outcome is different to the study of onabotulinum toxin A in idiopathic OAB patients where 90% of participants saw an improvement in FSFI score post treatment regardless of continence status (Miotla 2017).

A study by Ingber et al (2009) assessed the effect of sacral neuromodulation (SNS) for OAB on FSF. They found that SNS does not significantly improve female SF. However, a more recent study by Gill et al (2011) reported significant improvements in overall SF although this was not associated with improved lower urinary tract function. A further study by Yih et al (2013) looked at changes in SA follow SNS and found that 14% of women who had not previously been became SA following treatment. Overall however, for the women who had been SA throughout the study there was not a significant improvement in their SF post SNS.

Work by Musco et al (2016) evaluated the impact of percutaneous tibial nerve stimulation (PTNS) on FSD in women undergoing PTNS to treat their OAB symptoms. Using validated questionnaires they found that using PTNS improved SF in women.

A review by Proietti et al (2012) recommends that more therapeutic interventions, including new anticholinergics and other methods, in both men and women are needed to be able to evaluate the effect of OAB on sexual life.

Conclusions

OAB is a prevalent condition affecting the physical and psychological health of many women and presenting a wider economic burden. For those who do seek help, the evidence would indicate that assessment is essential to rule out underlying causes and clinical care should start with conservative therapies and if necessary drug treatment with antimuscarinics.

In this chapter I have described the impact OAB has on SF and reviewed the different methods of assessment and treatment available with a focus on antimuscarnincs and SF. One of the challenges identified during this literature review is that assessment of sexual function / dysfunction is varied amongst all the studies. There does not appear to be a set criteria for sexual activity and exactly what it entails. According to the new terminology report, assessment of sexual activity status should be self-defined and not limited to women who engage in sexual intercourse, but this definition is still subject to significant individual interpretation. All the studies use varying frequency of intercourse within their cohorts preventing reliable comparisons between studies. Standardised assessment and reporting methods for these clinical trials would help to overcome this.

Anticholinergics remain the mainstay of treatment, however, although there is a multitude of evidence available assessing efficacy in terms of reducing OAB symptoms, very little known about the impact of treatment on a woman's SF.

This has led to the development of the next chapter where a more in depth review of the impact of anticholinergics on SF has been performed.

Chapter 4

Do anticholinergics improve sexual function in women with overactive bladder syndrome?
A systematic Review

Introduction

According to Moher et al (2015), systematic reviews and meta analyses are the reference standard for synthesising evidence in health care due to their methodological rigor. They are not only used by clinicians to inform clinical decision making, but are often the starting point or supporting evidence used for clinical practice guidelines. Within the research setting, systematic reviews are also used to ensure that there is a justification for novel or further research in a particular field (Moher et al 2009).

At the start of this thesis, the area of interest was identified as the impact of treatment for OAB on women's sexual function. In order to gain an in depth understanding of the available literature, identify the knowledge gaps, develop and justify a research question, a systematic review was undertaken and is described in this chapter. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were published to provide a set of evidence based minimum standards for the reporting of systematic reviews to ensure quality and clarity and they have been utilised in the reporting of this review (Moher et al 2009).

Current Evidence Base

There is a large evidence base (Cochrane reviews, NICE guidelines etc) to support the use of anticholinergics and other treatment modalities in managing the urinary symptoms of OAB. However, in these reviews there are no references to the impact of anticholinergics and other treatments specifically on SF, yet this is an important and common problem encountered by many women with OAB as demonstrated in chapter 3.

To investigate in detail the sexual dysfunction of women with OAB and the impact of antimuscarinic drug therapy, this systematic review explores the

currently available literature regarding the use of anticholinergic medication, for the treatment of OAB on the SF of women.

To assist the search and to formulate a precise question, four parts to the clinical question were set using a PICO analysis. Table 4.1 demonstrates the PICO analysis set for this review.

Table 4.1 PICO analysis

Population	Sexually active women with OAB
Intervention	Anticholinergics
Comparison	No anticholinergics (including cohort studies comparing baseline to end of treatment)
Outcome	Sexual function

When setting these variables women included all females over the age of 18 who were SA. However, no limits were put on the frequency of SA within a defined period. The intervention of anticholinergics included all of the preparations currently licensed in the treatment of OAB that are available on the NHS. The comparison with no other anticholinergics (ie no treatment or placebo) allowed this search to be objective, avoiding comparisons regarding which individual anticholinergic drug had the largest impact on SF, but it addressed the effect of anticholinergics as a whole. Comparisons with conservative therapies such as lifestyle advice were accepted depending on the forms of therapies offered. The outcome was measured using data from validated questionnaires that have been designed to assess SF in women. From this analysis I formulated the following question for investigation:

Do anticholinergics improve SF in women with OAB?

Methods

Following the preliminary identification of my question, an initial scoping search was performed to ensure that a review of this question had not previously been performed or was currently in progress. The Cochrane Library held several reviews relating to anticholinergic medication in the treatment of OAB but none of these addressed SF. A scoping search on Medline was also performed and did not reveal any systematic reviews in the area. These initial searches confirmed the lack of evidence and the need for a review of the relevant data. From this I was able to formulate my search plan to assist in my search of the literature. A facet analysis was performed to identify keywords to be used in the search and variations of these terms that helped to ensure that all relevant literature was found. The facet analysis and search plan is shown in table 4.2.

Table 4.2 Facet analysis and search terms

Population	**Intervention**	**Outcome**
Women	Anticholinergics	Sexual function
Wom?n Females Adult	Antimuscarinics Darifenacin Fesoterodine Oxybutynin Propiverine Solifenacin Tolterodine Trospium	Sexual function$ Sexual dysfunction Relationship$ Marital relationship$
Overactive bladder Detrusor overactivity Detrusor instability Urinary incontinence		

($ and ? denotes truncations used in the search)

Searches were performed initially using the Cochrane library and then two further databases. Medline and Embase were chosen for this search so that studies from America and Europe would be included. The databases also hold studies from over 60 years ago. This was not necessarily relevant to this search as most of the anticholinergics currently available have been developed in the last fifteen years with the exception of one (oxybutynin) which has been available for over 30 years, however, it ensured that no seminal studies were missed. Keywords were used to search as MeSH terms and as free text. Boolean operators allowed searches to be combined and truncations (demonstrated by the ? and $ signs in the facet analysis) were used to ensure that the different variations of a word were also included in the search.

The generic names of each of the available anticholinergics were used in the search. Brand and trade names were not included as these differ around the world and may have led to important international papers being missed in the search.

Inclusion and exclusion criteria were set before the start of the search and are listed in table 4.3. These were set to limit the search to relevant studies that would help answer the research question and ensure that the data reviewed were of good quality. As the question outlined is looking at the effectiveness of an intervention, the ideal method to assess this would be randomized controlled trials (RCTs) or a systematic review. As the scoping search showed a lack of studies in this area, quasi-experiments and prospective cohort studies were also to be included to ensure sufficient data to review. Qualitative studies were excluded as the subjective nature of these studies means that validated outcome measures are not generally used and therefore there is no standardised way to assess SF among the population. Case reports and case series were also excluded as they are classed as level three evidence and do not meet the quality criteria for this review.

Table 4.3 Inclusion / Exclusion criteria

Inclusion Criteria	Exclusion Criteria
Written in English Women > 18 years Systematic reviews RCT's Quasi-experiments Prospective cohort / observational studies / pre-post intervention studies Using validated outcome measures Accessible online via KCL	Not written in English Unable to obtain full text Non validated outcome measures Qualitative studies Case reports

As the field of practice being reviewed is very specialised, searches were also performed on the ICS and IUGA database and ICI-RS website to find relevant abstracts that have been presented at international meetings, which may have led to publications. To ensure that I also identified any relevant grey literature, abstract books and urology / urogynaecology / SF textbooks were hand searched and clinical trial databases were reviewed. Once I had gathered all the relevant studies, I discussed the search with two Professor's (Professor Cardozo and Professor Norton) who specialise in this field of practice to ask if they were aware of any other sources of information or current trials in progress that would provide studies for this search.

Findings of the review

The search spanned from 1966-2011 and a small number of studies was identified. These included one systematic review, 18 RCT's, 5 comparative studies, 4 clinical trials, 2 journal articles and a conference abstract. Of these 30 studies, 16 were excluded on title alone and a further 7 were excluded after reading the abstract. For the 7 remaining studies the full text was read to assess their suitability for inclusion. Based on this a further 5 studies were excluded. The reasons for exclusions are listed in table 4.4.

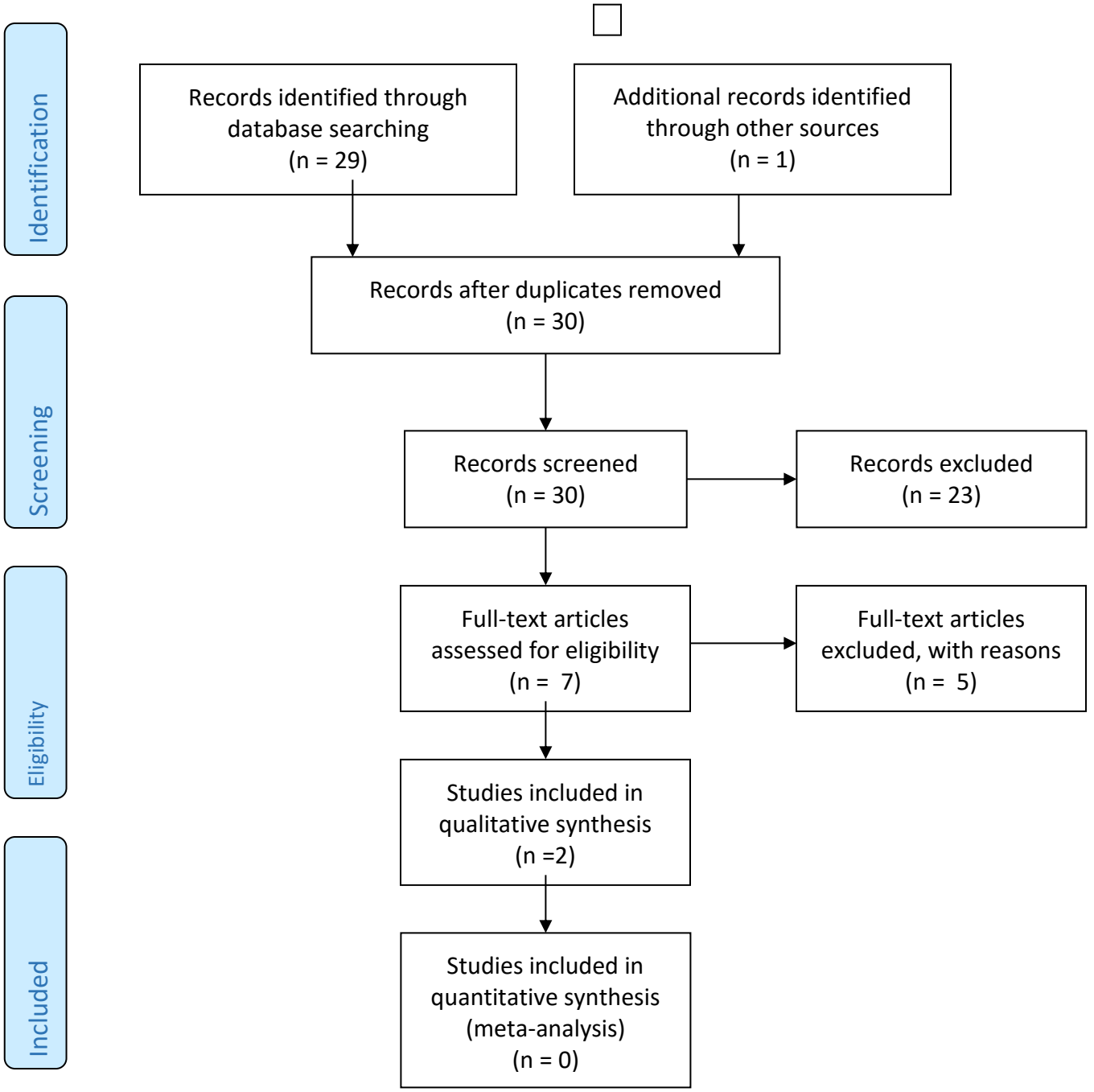
Figure 4.1 is a PRISMA flow diagram to demonstrate the findings of the review.

Table 4.4 Studies excluded after reading full text.

Study	**Reason for exclusion**
Rogers et al 2008	Contains the same cohort of patients as a study already included in review
Serati et al 2008	Assesses sexual function as a reduction in episodes of orgasm incontinence and not by a validated questionnaire
Khullar et al 2006	Reviews sexual function as part of health related quality of life and not as an individual outcome
Bachmann et al 2007	Abstract only from international conference same cohort of patients as study already included
Sand et al 2006	Study includes men and women and does not separate the results per gender group

Figure 4.1

PRISMA 2009 Flow Diagram



Two of the studies read met the inclusion criteria and will be critiqued for this review. The characteristics of these studies including the type of study, sample size, length of the study etc have been included in Table 4.5. The levels of evidence have been graded according to the levels set for intervention studies in the SIGN guidelines (2001).

Table 4.5 Characteristics of included studies

Authors and date	Hajebrahimi et al 2008	Rogers et al 2009
Study type	Open label Prospective observational study	12 week open label extension observational study
Population	Sexually active women with OAB	Sexually active women with OAB
Intervention	Tolterodine immediate release	Tolterodine extended release
Sample size	30	163
Length of intervention	12 weeks	24 weeks
Outcome measure	Arizona Sexual Experience Scale (ASEX)	Pelvic organ prolapse - urinary incontinence sexual questionnaire (PISQ) and Sexual quality of life female questionnaire (SQOL-F)
Comparison	Pre and Post treatment and at set time intervals during study	Placebo and pre and post treatment at set time intervals during study
Level of evidence	2+	1+
Funding	Pfizer Inc	Pfizer Inc

Description and Critical Appraisal of Included Studies

The SIGN critical appraisal checklist for an article describing a cohort study was used to guide the critique of the studies included in this review. The PRISMA checklist was also utilised.

Paper 1 Hajebrahimi et al 2008

In this study, the population included 30 women from Iran with a diagnosis of OAB aged between 20 to 32 years. Women who were NSA or in unstable relationships were excluded from the study. These women were not randomly selected from a defined population but were identified prospectively from a urogynaecology clinic, however it does not suggest how many women attending this clinic were unsuitable or declined participation. The intervention was tolterodine IR 2mg twice daily (bd) for a three month period. There was no control group or placebo arm in this study and comparisons were made from pre-treatment status to post treatment and at monthly intervals during the study. The outcome of this study was to evaluate the effect of tolterodine IR on the SF of women with OAB using the Arizona Sexual Experience Scale (ASEX) which had been validated for the Persian language. The ASEX scale assesses SF under five domains: - desire, arousal, vaginal lubrication, orgasm and orgasm satisfaction. Analysis was performed for each of these topics at baseline and at monthly intervals until the completion of the trial. Ethical approval was gained for this study and all patients provided written consent. As this was an open label study no blinding took place however there is no evidence to suggest selection or performance bias as all participants were assigned the same dose of medication for the length of the trial and treated equally throughout. However, as this study is not placebo controlled it is not possible to assess the potential of the placebo effect.

The paper reports that a McNemar test was performed to assess if the change in status of SF was statistically significant and this was predetermined at 0.05 point level. The study states that two patients did not

return for follow up but final analysis was performed on 28 subjects. Demographic characteristics of the subjects were reported. Rationale was provided for the choice of statistical methods used to analyse the data. Sexual dysfunction was defined by an ASEX score of 17 or above and this was set following a validation study.

Although this study only had a small number of subjects the methods reported are easily reproducible.

It could be considered that an RCT would have been a more robust methodology to evaluate the effect of tolterodine on the SF of this cohort. Firstly, this is because the process of randomization would ensure that the impact of all confounding variables are distributed equally within both groups. Secondly, it would allow the researchers to know the impact of the placebo effect that is observed when subjects enter a clinical trial and receive a package of care (even if they do not receive an active treatment) as a comparator. Within pre and post intervention studies such as the one reported in paper 1 (and later in paper 2) there is no comparison group. The difference that is measured is from the start to the end of the trial and therefore includes all the placebo effects within this. An RCT allows you to understand the effect of an intervention over and above the placebo effect, thus providing far more clinically relevant information. The challenge with this methodology, however, would be in the number of women that would need to be recruited as the population size would need to be considerably larger and this adds considerable expense and time to the study and it is likely that this would not be possible in a single center.

Paper 2 Rogers et al 2009

This study was a planned secondary analysis of data from a 12 week open label extension of a multi-center, double blind placebo controlled trial conducted in America. The first paper published from this study detailing the results from the original RCT has been excluded in this review as the same cohort of patients are included in the analysis of this paper and the original publication focused on the OAB outcomes of the study and not the SF data. In the 12 weeks of this trial, SA women over the age of 18 diagnosed with OAB and UUI were recruited from 54 outpatient sites across America. Extensive inclusion/exclusive criteria were set to ensure the appropriate population of women was observed in the study. Eligible women were randomised 1:1 in double blind fashion to placebo or tolterodine ER 4mg OD to be taken within four hours of bedtime for 12 weeks. A fixed block size of four was used to generate the randomisation schedule. This method and the double blinding ensured minimal selection bias. The primary outcome of this study was to evaluate the efficacy of tolterodine ER in treating the OAB symptoms in women with OAB and UUI. The secondary outcome was whether treatment of OAB symptoms was associated with improvements in sexual health. As multiple outcomes were investigated in this trial many different questionnaires were completed to evaluate these but I have not included a review of them all as they are not applicable to my research question.

SF was assessed using two validated questionnaires completed at baseline and at 12 weeks. The pelvic organ prolapse / urinary incontinence sexual questionnaire (PISQ) was used to assess SF in SA heterosexual women in three domains – behavioral / emotive, physical and partner related and the sexual quality of life questionnaire – female (SQoL-F), which assesses sexual quality of life and is validated in women with and without FSD. A power calculation was performed and recruitment was in line with this suggested sample size. In total 436 subjects were screened and 413 who meet the inclusion / exclusion criteria were randomised into the two arms (211 in the placebo group and 202 in the active treatment arm). There was

no evidence to suggest performance bias or that the two groups were treated differently throughout the course of the study. Analysis was completed on a total of 330 patients (based on a power calculation to assess OAB symptoms), 167 and 163 respectively demonstrating a follow up and completion rate of 81%. Reasons for withdrawal were included in the paper. Following this initial 12 week blinded period all patients then completed a 12 week open label extension. The primary aim of this part of the study was to assess if the improved outcomes that had occurred in the first 12 weeks of investigation persisted or improved with continued use to 24 weeks. Only women who had received 24 weeks of tolterodine ER were included in this analysis. Of the 163 women in this group, 161 completed the open label phase. Descriptions and rationale for statistical methods were provided in the paper. Ethical approval was gained from all participating centers and informed consent was obtained from all subjects.

The first phase of this RCT appears to have very robust methodology starting with a predetermined sample size from the power calculation and then encompassing double blinding, and a placebo controlled arm to the study. These factors helped to minimise bias in the trial and allowed the investigators to assess the placebo effect. However, assessment of SF was a secondary outcome and not the primary endpoint for this study and it is unknown if the power calculation and number of subjects is adequate to robustly assess this. By only assessing patients in the open label phase who had received 24 weeks of active treatment the investigators could observe continued or persistent improvements in symptoms over a longer time frame. If patients from the placebo arm who then initiated active treatment had been included it would not be possible to reliably assess the intended outcome of the extension study.

Results

The two included studies have used different outcome measures to assess SF. Although these are all validated scales it is difficult to combine the results of these studies in one table to assess the overall impact of anticholinergics on SF. Therefore the results of each study have been recorded separately in table 4.6 for paper 1 and table 4.7 for paper 2 and no meta-analysis was performed.

Table 4.6 reports the mean scores for each item in the ASEX scale from baseline and at each subsequent visit. Table 4.7 reports the mean improvement in scores of each domain on the PISQ and on the SQoL-F.

Table 4.6 Results from Hajebrahimi et al 2008

ASEX item	**Baseline**		**First follow up**			**Second follow Up**			**Third Follow up**		
	Mean	SD	Mean	SD	P value	Mean	SD	P value	Mean	SD	P value
Desire	4.1	0.923	3.39	1.44	0.01	2.86	1.113	<0.01	2.61	1.1	<0.01
Arousal	4	1.486	3.04	1.29	<0.01	2.46	0.999	<0.01	2.21	1.06	<0.01
Vaginal lubrication	3.43	1.278	2.79	1.37	0.0114	2.29	1.117	<0.01	2.21	1.13	<0.01
Orgasm	3.77	1.431	2.86	1.29	<0.01	2.64	1.283	<0.01	2.25	1.07	<0.01
Orgasm satisfaction	3.93	1.461	3.18	1.57	<0.01	2.75	1.43	<0.01	2.18	1.05	<0.01

With the ASEX, each topic is in a range of 1 (normal) to 6 (completely absent)

Paper 1

This study showed statistically significant improvements in all domains of the ASEX scale over the three month study period with most p values <0.01. Confidence intervals (CIs) were not reported in this paper but they could be calculated from the data provided. As an example the Arousal domain demonstrated the least change in ASEX score. At baseline patients reported a mean score of 4 (95% CIs 0.55 range 3.45-4.55) and this improved to a mean score of 2.21 at 12 weeks (95% CIs 0.4 range 1.81-2.61). The calculated CIs are very narrow and the ranges do not overlap suggesting in the absence of known minimal important difference, a high probability that the majority of patients did experience an improvement in levels of arousal after 12 weeks of treatment. Also at baseline 70% of subjects were classed as having sexual dysfunction compared to 16.3% after three months of treatment. This could be considered a clinically significant improvement in SF.

Table 4.7 Results from Rogers et al 2009

	Baseline		**Baseline to 12 weeks**			**12 – 24 weeks**			**Baseline to 24 weeks**		
	Mean	SD	Mean	SD	P value	Mean	SD	P value	Mean	SD	P value
PISQ Total	89.4	13.0	4.7	10.7	<0.05	0.8	6.0	0.14	4.9	11.3	<0.05
Behaviour Emotive	38.2	8.3	1.5	6.0	<0.05	0.2	4.2	0.53	1.7	6.5	<0.05
Physical	32.3	5.4	2.5	5.1	<0.05	0.5	2.9	<0.05	2.8	4.9	<0.05
Partner Related	19	2.9	0.6	2.2	<0.05	0.0	2.1	0.85	0.6	2.5	<0.05
SQoL – F	69.8	23.6	6.4	19.3	<0.05	1.3	10.3	0.13	8.7	20.3	<0.05

PISQ total scores range from 0 – 125: higher scores indicate better sexual function
SQoL-F scores range from 0-100: higher scores reflects better sexual quality of life.

Paper 2

This study showed statistically significant improvements in all domains of the PISQ and SQoL-F from baseline to 12 weeks and baseline to 24 weeks. However, from 12 to 24 weeks there was no further significant improvement in scores with the exception of the Physical domain, but initial improvements were maintained. Again this study did not include confidence intervals in the published data. Although, I did not calculate these for all the data in this table I looked at the results for SQol-F at baseline where the mean was 69.8 (95% CIs 3.65 range 66.15-73.45) to 24 weeks with a mean improvement of 8.7 (95% CIs 3.14 range 5.56-11.84).

In summary, both studies showed statistically significant improvements in SF as measured by their chosen questionnaire for patients on anticholinergic medication.

Limitations

The first limitation of this review is that the search did not reveal a great variety of studies that met the quality criteria set. , There were no RCT's identified to answer the research question. It could be considered that this may because it would be deemed unethical to leave the primary health condition (OAB) untreated in order to investigate a potential effect of treatment, when the efficacy and safety in treating the primary health condition has already been established. Potentially, the control group could be offered bladder retraining compared to bladder retraining and medication in the active arm, although the bladder retraining itself may have an effect on SF. Alternatively, a crossover design could be employed to overcome this, however, it is possible that the subjects would be able to identify which treatment they are on due to side effects of the treatment eg dry mouth and this may lead to difficulty in recruitment and retention to the study as women may not want to continue in the trial if they are not receiving active treatment and their symptoms continue to be bothersome. The lack of RCT's could also be because the impact of anticholinergics on sexual function and

subjects overall sexual health is not taken seriously or considered to be important enough to warrant the time, expense and multi-center co-ordination needed for such an investigation.

As the only studies identified in this review are pre and post intervention studies with no comparison groups, the quality of the evidence to identify the impact of anticholinergics was found to be low.

For a systematic review two independent assessors should be involved. This would help to rule out bias based on my preconceptions which may be wrong and my existing knowledge which may alter the inclusion / exclusion criteria to include other papers. However, in order to reduce this area for potential bias I tried to ensure that my search plan was explicitly set out and reproducible with regards to the studies identified and the data extracted. My facet analysis and search plan helped my search to be sensitive to identify the relevant information and specific to exclude irrelevant studies. Also the inclusion / exclusion criteria were set before the search as were the appraisal methods for the review to ensure that quality issues and standards were considered and a recognised structure for the appraisal was employed, thus improving the validity of the review.

This review explored studies using all the antimuscarinics currently available on the UK market. It is acknowledged that there may be data missing from trials using drugs that are no longer available eg terodiline which was commonly used as a treatment of OAB for many years but was withdrawn from the market in 1991 due to cardiotoxicity.

Qualitative data were excluded from this review, however, during the literature searching it was noted that a lot of research on SF uses qualitative outcomes. This could mean that a lot of useful information was missed, however, as qualitative research may not be generalisable, comparisons could have been invalid. In the future, a separate review of all the qualitative outcomes would be useful to enhance knowledge and understanding in the field.

For the studies that were reviewed, the anticholinergic used in the treatment arms was the same drug but just different preparations. Although, this would be a positive finding if my research question had been 'Does tolterodine improve SF in women with OAB?' It does not help me to reliably answer my question on anticholinergics as a class of drugs, as there is no evidence on any of the other anticholinergics available. Possible explanations for this could be publication bias if the results of other trials were equivocal or detrimental, and the impact on the pharmaceutical industry who would not want data released that shows that their product is not effective. It is also a possibility that my research question is too broad and if I was to make it more specific I may have gained sufficient evidence to be able to make recommendations for best practice.

The different outcome measures used in each study also made it difficult to appropriately compare the results between the trials and a meta-analysis was not possible. Although SF was measured using validated questionnaires, each of these does have its own limitations. For example the ASEX scale does not assess levels of distress caused by the urinary symptoms but the PISQ does. Also the scales measure different domains of SF so these cannot be individually compared. It was therefore only possible to compare overall improvement in scores in each individual study.

Many of the studies initially identified used validated QoL questionnaires that had a single item score assessing SF as part of general QoL. Although, inclusion of these studies may have garnered a lot more data, many of the publications do not provide the individual item scores but a total QoL score meaning that specific data regarding SF cannot be elicited. Also, as the focus of this review was SF, it was considered that only SF specific outcomes should be included to ensure quality, rather than any QoL outcome that may mention SF. However, given the lack of data using SF specific outcomes, it could be useful to assess the more generic measures to get an overview of the issue.

Excluding non-validated outcome measures resulted in many early studies being missed as it was not routine to use validated subjective outcome measures and researchers developed their own tools. However, this would have compromised the quality of the review, and results would not have been comparable.

Conclusions

Following appraisal of the relevant studies I do not think that there is sufficient evidence to answer my research question. Although, the two studies report statistically significant improvement in the SF of women with OAB with anticholinergics, I feel that there are too many limitations to the evidence and I do not feel that the data have great clinical significance. Therefore, I would suggest that the review uncovered the need for more data on the effectiveness of this intervention in clinical practice.

Considering that this is an area that has a significant impact of women's QoL, my final recommendation for this review is the need for high quality research in this area, focusing on SF as the primary outcome and adopting a standardised outcome measure so that improvements could be compared to others studies looking at different anticholinergics with similar designs.

Update of the literature

As the initial systematic review was performed at the start of this PhD pathway, I can no longer assume that it is valid. Therefore a 2017 update to the review entailed the replication of the literature search performed in 2011 using the same methods previously discussed.

The search yielded a small volume of new studies published from 2011 - 2017. Most of these were review articles and excluded after reading the abstract. One study was excluded after reading the full text (see table 4.8) and one further study was included in the review, the characteristics of which have been reported in table 4.9.

Table 4.8 Studies excluded after reading full text – 2017 update.

Study	Reason for exclusion
Chughtai et al 2016	Study assesses the combined effect of antimuscarinics and topical oestrogens on sexual function

Table 4.9 Characteristics of included studies – 2017 update.

Author and date	Jha 2016
Study type	Prospective observational questionnaire study
Population	Sexually active women with OAB
Intervention	Tolterodine, solifenacin, oxybutynin and Kentera patch
Sample size	34
Length of intervention	6 months
Outcome measure	Electronic Pelvic Assessment Questionnaire – Pelvic Floor (ePAQ-PF), Pelvic organ prolapse - urinary incontinence sexual questionnaire short form (PISQ-12) and Patient Global Impression of Improvement (PGI-I)
Comparison	Pre and Post treatment and at set time intervals during study
Level of evidence	2-
Funding	Pfizer Inc and grant from BSUG's and BAUS

Description and Critical Appraisal of Included Studies

Paper 3 Jha 2016

In this study, the population included 34 women from Sheffield with a symptomatic diagnosis of OAB. The mean age was 40.9 years however, the range was not provided. The majority were Caucasian (88%) and pre-menopausal (80%). Women were identified by the author by review of referral letters to secondary care and were asked to complete the ePAQ-PF as part of routine practice.

The ePAQ-PF is an electronic Pelvic Floor Assessment Questionnaire that is an interactive, web-based HRQL Questionnaire. It assesses four dimensions - urinary, bowel, vaginal and sexual symptoms and their related impact. It has undergone extensive psychometric testing. On completion, the four dimensions are further subdivided into 19 clinical domains, one of the urinary domains is OAB, and the sexual dimension provides three domain scores related to pelvic floor symptomatology that may impact SF including urinary, bowel and vaginal. Each domain has an associated score ranging from 0 (best health status) to 100 (worst health status). Women who scored over 33% bother on the OAB domain of the urinary dimension and the urinary domain of the sexual function dimension were invited to participate in the study. All patients were treatment naive in relation to starting anticholinergic therapy. Exclusion criteria were noted including the presence of POP and voiding dysfunction. Ethical approval was obtained for this study but there is no mention on the method of consent by participants.

The intervention was either tolterodine, solifenacin, oxybutynin or oxybutynin patches. No information is provided as to whether the tolterodine and oxybutynin were the immediate release or modified release preparations and there is no breakdown to notify how many women received each different treatment or why the decision was made to use each treatment. Although this is an open label study and no blinding took place, the women received different treatments and potentially different doses (as no information

regarding dose escalation is provided in the paper) there is the potential for selection and performance bias in the study. There was no control group or placebo arm in this study and comparisons were made from pre-treatment status to post treatment and at three monthly intervals during the study.

The PISQ-12 was used to assess SF in three domains – behavioral / emotive, physical and partner related. In this study a 20% improvement in total PISQ-12 scores was considered clinically significant. The PGI-I was used to establish treatment response. It asks women to rate the outcome from 'very much worse' to 'very much improved' over a 7 point Likert scale. The outcome of this study was to establish whether an improvement in OAB symptoms by treatment with anticholinergics is associated with corresponding improvement in SF.

A power calculation was performed based on a clinically significant change in PISQ-12 scores and recommended that 74 participants (allowing for a 20% drop out rate) would be required to take each different anticholinergic to prove the effectiveness of individual anticholinergics. It was suggested that a large multicenter trial was necessary to recruit this number of women so this paper was classed as a pilot feasibility study.

The statistical plan aimed to analyse and establish the impact of a 20 point improvement in OAB symptoms and correlate to changes in SF. Rationale was provided for the choice of statistical methods used. Significance was set at a p value of <0.05. Analysis was completed on 24 of the 34 women recruited, reasons for withdrawal were not included in the paper.

There are a lot of details missing in the methodology to make this study reproducible and it seems to be more an assessment in real world practice rather than the controlled conditions of a clinical trial. Although, understanding how women respond to treatment outside of a clinical trial setting can be hugely valuable, due to variations in practices it means that the results may not be generalisable to all care settings.

Results

Paper 3 Jha 2016

This study used different outcome measures from the two previous studies so cannot be combined and has been recorded separately in table 5.10. The only outcome provided was the mean PISQ-12 scores at baseline and at 3 and 6 months post commencement of treatment (Table 4.10). Meta-analysis is still not possible as the search is still unable to identify the minimum requirement of 2 relevant RCT's to answer the research question.

Table 4.10 Results from Jha 2016

	Baseline PISQ-12	**3months PISQ-12**	**6months PISQ-12**
All women	30.15	30.25	39.5
Postmenopausal women	30.5	35.0	36.0

Range 0-48

This study showed no significant improvement in PISQ-12 scores pre and post treatment with a p value of 0.909 at 3 months and 0.458 at 6 months. A secondary analysis was performed following exclusion of the post-menopausal women but this still did not reveal any statistically significant difference. There was no association between any of the PISQ-12 domains to changes in OAB scores following treatment demonstrated. 16/24 (67%) women reported an improvement in OAB symptoms on anticholinergics but only 8% reported an improvement in SF. Improvement in OAB symptoms were not associated with an improvement in SF. Confidence intervals were not reported in this paper and could not be calculated from the data provided.

In summary, this study did not find any statistically significant improvement in SF for women taking anticholinergics for OAB symptoms, in comparison to their pre-treatment state.

Conclusions

Having repeated this literature review six years later, there is still limited and insufficient evidence to answer the research question. The outcomes of the additional paper conflict with the findings of the two previous studies.

Potentially, this is because of the different anticholinergics used. The first review may have shown a positive effect of a single anticholinergic medication, whereas the Jha paper considered the effect of anticholinergics as a class of drugs rather than the individual compounds. However, the Jha paper does appear to have an increased risk of bias compared to the two earlier papers due to the methodology so this may also have an impact on the outcomes.

The previously noted limitations of the study remain unchanged in the update as I was still the only assessor of the evidence, and each paper used different outcomes making comparisons difficult. However, the explicit criteria, search terms and methods originally set allowed for an easily reproducible updated review of the literature which has reiterated the lack of high quality evidence when assessing the impact of anticholinergics on the SF of women with OAB.

This confirmation of the knowledge gap justifies the need for further research in this area and from a methodological consideration the investigation of a single compound appears to introduce less bias to a study. These findings, in combination with the grant approval from Pfizer (and supply of study drug led to the development of the research question discussed in the next section of this thesis:-

'Does fesoterodine have any effect on the sexual function of women with OAB?'

PRISMA Checklist

Section/topic	Item No	Checklist item	Reported on page No
Title			
Title	1	Identify the report as a systematic review, meta-analysis, or both	96
Abstract			
Structured summary	2	Provide a structured summary including, as applicable, background, objectives, data sources, study eligibility criteria, participants, interventions, study appraisal and synthesis methods, results, limitations, conclusions and implications of key findings, systematic review registration number	n/a as chapter not review article
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known	96
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS)	97
Methods			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (such as web address), and, if available, provide registration information including registration number	no
Eligibility criteria	6	Specify study characteristics (such as PICOS, length of follow-up) and report characteristics (such as years considered, language, publication status) used as criteria for eligibility, giving rationale	99
Information sources	7	Describe all information sources (such as databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched	99
98Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated	98
St101udy select103ion	9	State the process for selecting studies (that is, screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis)	101
Data collection process	10	Describe method of data extraction from reports (such as piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators	103
Data items	11	List and define all variables for which data were sought (such as PICOS, funding sources) and any assumptions and simplifications made	103
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis	103

Section/topic	Item No	Checklist item	Reported on page No
Summary measures	13	State the principal summary measures (such as risk ratio, difference in means).	104
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (such as I^2 statistic) for each meta-analysis	108
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (such as publication bias, selective reporting within studies)	107
Additional analyses	16	Describe methods of additional analyses (such as sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified	n/a
Results			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram	102
Study characteristics	18	For each study, present characteristics for which data were extracted (such as study size, PICOS, follow-up period) and provide the citations	103
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome-level assessment (see item 12).	105
Results of individual studies	20	For all outcomes considered (benefits or harms), present for each study (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot	108
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency	n/a
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see item 15)	110
Additional analysis	23	Give results of additional analyses, if done (such as sensitivity or subgroup analyses, meta-regression) (see item 16)	n/a
Discussion			
Summary of evidence	24	Summarise the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (such as health care providers, users, and policy makers)	110
Limitations	25	Discuss limitations at study and outcome level (such as risk of bias), and at review level (such as incomplete retrieval of identified research, reporting bias)	110
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research	118
Funding			
Funding	27	Describe sources of funding for the systematic review and other support (such as supply of data) and role of funders for the systematic review	n/a

Chapter 5

Fesoterodine Fumarate

Introduction

The literature review presented in Chapter 4, showed that there is a knowledge gap in our understanding of the impact of anticholinergics on SF and that this thesis would focus on developing a clinical trial to further investigate this area. This chapter will focus on fesoterodine which was the anticholinergic selected for use in the clinical trial described in Chapters 6-10. Fesoterodine is the newest antimuscarinic agent available on the UK Pharmaceutical market. It gained marketing approval in 2007 and was launched in 2008 and is available as sustained release tablets in flexible once daily dosing (4mg and 8mg). It was developed and marketed by Pfizer Ltd until 2015 when Pierre Fabre took over the marketing.

As discussed in Chapter 1, fesoterodine was selected for convenience as at the time there was opportunity for research grants where it was new to market and an IIR was awarded by Pfizer to fund this work and supply all study medication. This chapter provides an overview of the pharmacodynamic and pharmacokinetic properties of fesoterodine and the evidence available for its use in the management of OAB.

Pharmacodynamic properties

Fesoterodine is isobutyric acid 2-((R)-3-diisopropylammonium-1-phenylpropyl)-4-(hydroxymethyl) pheyl ester hydrogen fumarate. The empirical formula is $C_{30}H_{41}NO_7$. The structural formula is shown in figure 5.1 (Taken from Rantell et al 2014).

Fesoterodine functions as an orally active prodrug that is rapidly hydrolysed to its active metabolite 5-hydroxymethyltolteroine (5-HMT) by non-specific esterases (Cole 2004). The parent drug fesoterodine is not a potent antimuscarinic; its antimuscarinic activity results from the active metabolite (5-HMT) which is a balanced muscarinic receptor blocker without selectivity for any particular muscarinic subtype (Nilvebrant 1997).

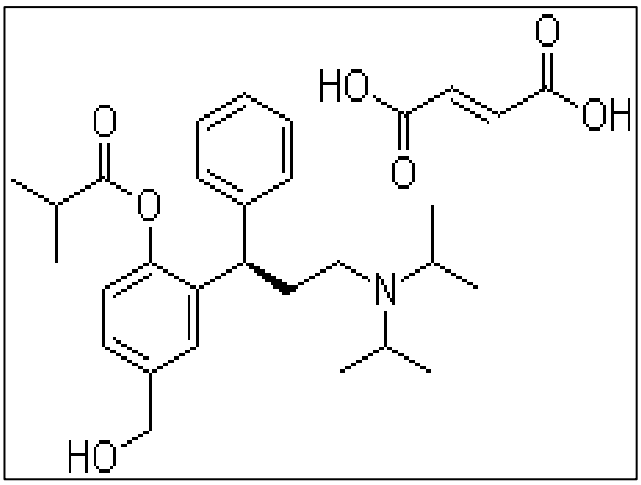


Figure 5.1 The chemical structure of fesoterodine.

Fesoterodine is the sister drug of tolterodine which has been used for the treatment of OAB for over 20 years and was the market leader for the majority of this time. Tolterodine is available as an immediate release (IR) preparation at a dose of 1mg and 2mg and as an extended release (ER) preparation at a single dose of 4mg. Both fesoterodine and tolterodine share the same active metabolite but how the 5-HMT is generated differs between the two.

Pharmacokinetic properties

Tolterodine is converted to 5-HMT by the cytochrome P450 2D6 enzyme system (CYP 2D6) (Nilvebrant 1997). Tolterodine has antimuscarinic activity similar to that of 5-HMT however fesoterodine is inactive and undetectable in plasma after oral dosing therefore functioning as a prodrug of 5-HMT (Simon and Malhotra 2009).

Hydrolysis to its active metabolite bypasses the hepatic CYP pathway (Vella 2011). 5-HMT then requires liver involvement for its biotransformation and elimination via the CYP 3A4 and CYP 2D6 isoenzymes (Cole 2004). The pharmacokinetic properties of 5-HMT are independent of sex or age (Malhota 2009a).

Studies have been performed assessing the effects of hepatic dysfunction and renal impairment on the pharmacokinetic (PK) profile of fesoterodine. De May et al (2010) conducted a prospective, open label, parallel group, single dose trial of the PK of 5-HMT and its metabolites after administration of fesoterodine 8mg to subjects with hepatic cirrhosis and matched healthy controls. They reported that fesoterodine 8mg was well tolerated in patients with hepatic cirrhosis and based on these results the product label specifies that fesoterodine is safe in subjects with moderate hepatic impairment. Malhotra (2009b) performed an open label, parallel-group, single-dose trial with administration of fesoterodine 4mg in subjects with renal impairment compared to healthy subjects. It was reported that fesoterodine 4mg was well tolerated in healthy subjects as well as subjects with mild, moderate or severe renal impairment. However, it is recommended based on their findings that only patients with mild or moderate renal impairment should be dose increased to fesoterodine 8mg if clinically necessary.

Subsequent studies have evaluated the effect of fesoterodine in conjunction with warfarin and fluconazole. Malhotra (2011a) reported that the pharmacokinetics and pharmacodynamics of warfarin 25mg in health adults are unaffected by fesoterodine 8mg and that co-administration of warfarin and fesoterodine is safe and well tolerated. Malhotra et al (2011b) looked at whether dose adjustment is necessary when fesoterodine is administered with a moderate CYP3A4 inhibitor. They used fluconazole to assess this and found that adjustment of fesoterodine dose is not warranted when co administered with a moderate CYP3A4 inhibitor.

Flexible dosing and treatment schedules

Staskin et al (2010) performed a post hoc analysis on data from two randomised, double blind, placebo controlled, 12-week Phase III trials in which 1674 subjects were treated with morning doses of fesoterodine 4mg, 8mgs, or placebo. Their objective was to evaluate the efficacy of fesoterodine versus placebo over selected intervals during a 24-hour period. They divided the day into three 8-hour time intervals, daytime (08.00-15.59),

evening (16.00-23.59) and night-time (00.00 – 07.59) and assessed changes in the number of micturition's, urgency episodes, UUI episodes and mean volume voided (MVV). The results showed that at the end of treatment the mean change from baseline for all efficacy endpoints were significantly greater with fesoterodine 4mg and 8mg compared to placebo during each 8-hour time interval. There was also a significantly greater improvement in the number of UUI episodes and number of micturitions with both fesoterodine doses versus placebo at each time interval. They concluded that fesoterodine 4mg and 8mg given once daily demonstrated efficacy over placebo during all three time intervals supporting once daily dosing.

Malhotra (2009c) investigated whether fesoterodine should be taken in the morning or in the evening and if there were any diurnal variations in the pharmacokinetics of fesoterodine. This was achieved through a randomised, open label, two period, two treatment crossover, single-dose study, where 14 healthy subjects received daytime and night-time oral dosing of fesoterodine 8mg and blood samples for 5-HMT PK determination were collected at specified intervals before and after dosing. They found that plasma concentration versus time profiles were equivalent for daytime and night-time supporting administration at either time.

There have been many studies looking at the dosing of fesoterodine, when it should be taken and the importance of flexible dosing. This is because individuals differ in their sensitivity to drug treatment due to a combination of pharmacodynamics and pharmacokinetic reasons (Michel & Staskin 2011). Dose titration is important for selection of the more effective dose of treatment which is associated with minimal side effects. In a study by Cardozo et al (2012) looking at flexible dosing 59% of patients opted to dose escalate after four weeks of treatment with 93% of escalators stating that this decision was based on insufficient clinical response.

In 2010, Wyndale et al reported a post hoc analysis of data from a 12-week, open label, flexible dose study to assess changes in OAB symptoms and patient reported outcomes and stratified their data according to whether the

patients opted for dose escalation. They found that 50% of patients opted to dose escalate at week 4 of treatment and those patients who opted to dose escalate had significantly higher means for all bladder diary variables except UUI episodes. The group of dose escalators also had significantly lower health related quality of life (HRQL) scores at baseline suggesting that they were significantly more bothered by their bladder symptoms than the non-escalators. At 12 weeks, both groups reported significant improvements in all outcomes and there were no significant differences between escalators and non-escalators. However, the escalators had significantly greater improvements in urgency episodes and total HRQL scores. They surmised that flexible dose fesoterodine significantly improved OAB symptoms and patient reported outcomes in subjects who stayed on the initial 4mg dose as well as the 50% who chose to dose escalate. They observed that those who chose to dose escalate reported more severe symptoms at baseline and that this group had fewer improvements than non-escalators before dose escalation. It was suggested that these findings may help clinicians to identify patients who are more likely to require fesoterodine 8mg to achieve maximum relief of symptoms and facilitate dose escalation in these patients.

Following on from the Wyndale study, Cardozo et al (2010a) investigated whether the severity of baseline UUI can predict dosing requirement. This was a pooled analysis of data from two double blind, placebo controlled trials where patients were randomised to fesoterodine 4 or 8mg or placebo for 12 weeks. The subjects were stratified into tertiles (>0-<2, 2-<4, or >4) according to the number of UUI episodes per day reported at baseline and compared at the end of treatment. It was reported that fesoterodine 4mg and 8mg significantly reduced UUI episodes compared to placebo and that the effects appeared to be greater in the 8mg group. It was suggested that clinical identification of patients could be used to assist in the decision as to who would benefit most from dose escalation.

Cardozo et al (2010b) developed a predictive model for dose response relationships to describe the effects of fesoterodine in patients with OAB. They used data collected from double blind placebo controlled phase II and

III trials to develop longitudinal dose response models. The models predicted that within 3-4 weeks after treatment initiation, clinically significant and near-maximum treatment effects would be seen. They found that there was a consistent dose response for fesoterodine in bladder diary endpoints supporting the greater efficacy of fesoterodine 8mg. It was suggested that this model could be used to predict outcomes for doses not studied and for under-represented patient sub groups in clinical trials.

In 2014, Wyndale et al performed a systematic review of dose escalation data from flexible dose studies. 10 studies were reviewed and overall, 51-63% of patients opted to dose escalate in clinical trials with efficacy cited as the main reason. Escalators generally reported more severe symptoms and impact on QoL. They concluded that the true dose response effect demonstrated in the studies provides treatment benefit to patients with OAB and recommends dose escalation to 8mg in individuals who require additional efficacy benefit.

Overall, all of these studies support once daily dosing of fesoterodine and resulted in the prescribing regulations suggesting that all patients start on 4mg daily and this can be escalated to 8mg daily if necessary and tolerated after four weeks.

Treatment response and UDS variables

A study was performed by Nitti et al (2009) to determine whether the presence of DO in patients with OAB and UUI is a predictor of the response to fesoterodine. They designed a phase 2 randomised, multicentre, placebo controlled trial with a one week placebo run in phase followed by an eight week double blind period. 210 patients were stratified into two balanced groups depending on the outcome of their baseline UDS assessment. They found that there were no significant differences in treatment responses between patients with and without DO. It was concluded that regardless of the presence of DO, patient's response to fesoterodine was dose

proportionate ie increasing the dose led to greater symptom improvement and is independent of the UDS diagnosis.

In contrast a smaller study (n=79) by Kim et al (2011), looking at predictors of response to fesoterodine in patients with OAB, showed that more patients who reported improvement post treatment were found to have DO on UDS pre-treatment.

A study by Winkleman et al (2017), suggests that responses to treatment with fesoterodine are not related to UDS variables but related to increasing age, higher parity and marital status (being married).

Efficacy, tolerability and safety of fesoterodine

There have been several studies looking at the early onset of efficacy for patients taking fesoterodine. Goldman et al (2010) assessed the efficacy of fesoterodine 4mg after one week of treatment. This was a pre-specified analysis collected during the first week of a 12 week, open label, single arm, flexible dose study of fesoterodine involving 516 subjects. These patients had all been previously treated with tolterodine or tolterodine ER and been dissatisfied with treatment. They reported that there were significant improvements in all bladder diary variables at the earliest point of assessment after one week of treatment with fesoterodine 4mg and the diary dry rate was 38% (this relates to the number of patients who at baseline reported UUI episodes but did not at one week). It was concluded that fesoterodine 4mg showed a rapid onset of efficacy at one week.

Corcos et al (2011) performed a study to assess the onset of efficacy of fesoterodine 4mg versus placebo. This analysis was from data collected during the first week of a 12 week double blind trial. Eligible subjects were randomised to fesoterodine 4mg, tolterodine ER 4mg or placebo. Only patients who had received fesoterodine or placebo were included in this analysis which totalled 936 subjects. They found that fesoterodine 4mg was associated with significantly greater improvements compared with placebo in

several endpoints including number of micturitions, UUI episodes and dry rates. They also reported that these differences were significant as early as day 5 of treatment. Their findings agreed with the Goldman study (2010) which states that patients receiving fesoterodine 4mg may expect to experience a response as early as one week after initiating treatment. Although this observed early effect may be due to the pharmacokinetics of fesoterodine and its ability to reach its therapeutic window rapidly, however, it could also be postulated that by asking patients to monitor their symptoms regularly and complete multiple bladder diaries there may be a cognitive effect (similar to the principles of bladder retraining) that may also lead to reductions in bladder diary variables. It would have been useful in these studies to have some blood samples assessing PK values to confirm or refute the rapid onset of action.

There have also been many studies looking at the efficacy and tolerability of fesoterodine. In 2009, Sand et al performed a post hoc analysis of pooled data from two clinical trials which included 1,548 women with OAB who were randomised to placebo, fesoterodine 4mg or 8mg or tolterodine ER 4mg for 12 weeks. Three day bladder diaries and treatment response were rated at baseline, 2 weeks and 12 weeks. They found that fesoterodine 8mg was significantly more efficacious than fesoterodine 4 mg, tolterodine 4mg and placebo in improving UUI episodes and continent days per week.

A similar post hoc analysis of a phase III clinical trial had previously been undertaken by Chapple et al (2008) to compare improvement in OAB symptoms and HRQL in patients taking fesoterodine 8mg and tolterodine 4mg. Although both groups showed statistically significant improvements in bladder diary variables and treatment response rates, those on fesoterodine again had greater improvement in UUI episodes and number of continent days.

Kraus et al (2010), looked at the efficacy and tolerability of fesoterodine in older and younger subjects with OAB. This involved data from two randomised, 12 week studies of 1681 adults who were treated with

fesoterodine 4mg, 8mg or placebo and these data were stratified by age. All patients completed 3 day bladder diaries at 3 points in the study, treatment response scales and a King's Health Questionnaires (KHQ) which is a disease specific questionnaire for assessing men and women with LUTS. It comprises nine domains, one of which is personal relationships. They divided the patients into three groups, those under 65 years, the second group were 65-75 years and finally those over 75 years. They found that in the under 65 year group, fesoterodine 4mg and 8mg was associated with statistically significant improvements at week 12 versus placebo in the bladder diary variables. However, fesoterodine 8mg provided greater improvements in UUI episodes compared to 4mg. For the middle group (65-75 years), they experienced significant improvements in most diary variables with fesoterodine 4mg and 8mg versus placebo. In the older group (>75 years), fesoterodine 8mg significantly improve all diary variables except for mean voided volume versus placebo. However, there were no statistically significant improvements between fesoterodine 4mg and placebo. They also reported that the >75years group had more adverse events including dry mouth and constipation but this did not increase the discontinuation rate. They concluded that fesoterodine 4mg and 8mg was efficacious in patients aged <75years but only fesoterodine 8mg was effective in those over 75years.

A double blind, placebo controlled, Pan European trial assessing fesoterodine treatment in older people with OAB was performed by Wagg et al (2011). All 794 subjects were over 65yrs with a mean age of 72yrs. They found that fesoterodine was well tolerated in these elderly subjects and was associated with statistically and clinically significant improvements in urgency episodes, number of micturitions and patient reported outcomes.

The long-term safety, tolerability and efficacy of fesoterodine was assessed by Scarpero et al (2011). They performed a post hoc analysis of data pooled from two open label extensions of double blind studies. In these, all subjects began open label treatment with fesoterodine 8mg and had the option to voluntarily dose reduce to 4mg and re-escalation to 8mg permitted once

annually. Maximum duration of treatment ranged from 24-36 months. A total of 439 out of 890 subjects (83 men and 356 women) continued open label treatment for >24 months. Statistically significant improvements in UUI episodes, number of micturitions and MVV between double blind baseline and open label baseline were sustained and further improved through to month 24. They concluded that long term fesoterodine was well tolerated and associated with sustained improvements in OAB symptoms in men and women.

In 2009, Wyndale et al investigated the efficacy and tolerability of flexible dose fesoterodine in patients who were dissatisfied with previous tolterodine treatment. This was a 12 week, open label study which recruited 516 adults. Fifty percent of subjects opted to dose escalate at week 4 and endpoints were assessed using bladder diaries as well as the Patient Perception of Bladder Condition (PPBC), the Overactive Bladder Questionnaire (OAB-q) and a Treatment Satisfaction Questionnaire (TSQ). They found that at the end of 12 weeks 80% were satisfied with treatment and there were significant improvements from baseline in the PPBC and in HRQL.

The SAFINA (UK Study Assessing Flexible Dose Fesoterodine in Adults) was an open label, flexible dose study of patients in the UK to assess the efficacy, tolerability, safety and patient reported treatment satisfaction (Cardozo et al 2010c). They found that 74% of subjects reported treatment satisfaction after 12 weeks of therapy with fesoterodine. They also performed exploratory analyses to understand the impact of cessation of fesoterodine after 12 weeks of therapy, showing that for all bladder diary variables there was significant deterioration in symptoms four weeks later.

Many trials have looked at the impact of fesoterodine on patient's QoL. Kelleher et al (2008) pooled data from two randomised placebo controlled phase III trials and evaluated the effect of fesoterodine on HRQL in patients with OAB. In these studies patients were randomised to placebo, fesoterodine 4mg, fesoterodine 8mg, or in one trial, tolterodine ER 4mg for a period of 12 weeks and patients completed the KHQ. In total 1669 patients

completed these studies. The fesoterodine 8mg group had statistically significant improvements over placebo in eight of the 9 KHQ domains including the personal relationship domain. Fesoterodine 4mg and tolterodine showed statistically significant improvements over placebo in seven of the nine domains of the KHQ but this did not include personal relationships. A further study by Kelleher et al (2012) evaluated sustained improvement in patient reported outcomes during long term fesoterodine treatment. This was a pooled analysis of two open label extension studies of 864 subjects. It found that treatment with fesoterodine for up to 24 months resulted in sustained improvement in measures of HRQL and severity of bladder related problems. They concluded that long term treatment with fesoterodine is beneficial to patients with OAB.

The two biggest studies using fesoterodine are the FACT studies. This stands for Fesoterodine Assessment and Comparison versus Tolterodine. FACT 1 (Herschorn et al 2010a) was the first head to head, placebo controlled trial with the primary objective of assessing superiority of fesoterodine 8mg over tolterodine ER 4mg. Subject were randomised to one of three arms (fesoterodine 4mg for one week then 8mg for 11 weeks, tolterodine ER 4mg or placebo with a sham dose escalation after one week in the tolterodine and placebo arm). FACT 2 (Kaplan et al 2011) was the largest placebo controlled head to head superiority study of antimuscarinics designed to make predefined comparisons for both diary based measures and patient reported outcomes. 1712 subjects were enrolled into FACT 1 and 2417 subjects to FACT 2. These studies showed that fesoterodine 8mg was superior in efficacy to tolterodine ER 4mg and placebo in reducing UUI episodes as well as other bladder diary variables and in improving patient reported outcome measures.

The outcome measure used was the OAB-q. This is a validated tool assessing symptom bother and HRQoL. It is split into four domains. One of these is based on social interaction and includes items on partners and spouses. Improvements in OAB-q scores from baseline to week 12 were significantly greater in the fesoterodine group than the placebo group. In a

post hoc statistical comparison, improvements from baseline to week 12 in the fesoterodine group were also significantly greater than in the tolterodine ER group.

In 2010, Gupta et al, performed a review of the literature for the use of fesoterodine for OAB. They reviewed a total of 20, phase II, III and IV trials and concluded that fesoterodine is an efficacious and well tolerated treatment option for patients with OAB. This was updated in 2012 (Dell'Utri et al 2012) and added that the once daily flexible dosing regimen is an appealing factor in clinical decision making.

Weiss et al (2013) looked specifically at the effect of fesoterodine on nocturnal urgency and found a significant reduction in nocturnal urgency episodes compared to placebo.

One criticism with clinical trials is that often results and conditions involved do not correlate with routine clinical practice. Kim et al (2016) performed a study using fesoterodine in over 3000 patients in clinical practice in Korea as a post marketing surveillance and confirmed that fesoterodine is a well-tolerated and effective treatment for patients in routine practice with OAB.

A recent review in primary care in Spain, reported that at twelve months, persistence with fesoterodine was greater than with two other common antimuscarinic agents (solifenacin and tolterodine) and resulted in the reduced need for concomitant medication (Sicras-Mainar et al 2016).

Fesoterodine and special populations

In 2012, Sand et al, published a pooled analysis of two open label extension studies to review the long term safety, tolerability and efficacy of fesoterodine stratified by age. They reported that long term fesoterodine was well tolerated and irrespective of age provided sustained improvements in OAB symptoms.

There have been several studies specifically looking at the impact of fesoterodine in the older and frail populations. The SOFIA study by Wagg et al (2013) was a 12 week, randomised, double blind placebo controlled study that assessed the efficacy and safety of flexible dose fesoterodine in elderly adults. 794 men and women took part in the study and 71% opted for dose escalation. Fesoterodine was associated with significantly greater improvements in most bladder diary variables and PROMs and was generally well tolerated.

DuBeau et al (2014) evaluated the efficacy and safety of fesoterodine in 562 complex vulnerable elderly subjects with UUI in the community. Participants within this trial had a high level of comorbidities, polypharmacy and functional impairment. However, fesoterodine was found to significantly improve UUI and QoL and most other diary variables. There was no deterioration in the mean Mini Mental State Examination (MMSE) seen in this study and work by Kay et al (2012) also confirmed that fesoterodine at both doses had no statistically significant effect on any cognitive function assessed including memory.

Following a systematic literature review and international consensus validation process on the appropriateness of oral drugs for long-term treatment of LUTS in older persons, Fesoterodine was the sole anticholinergic to be given a Grade B recommendation (all others graded C or D) however, it should be noted that this process was funded by Pfizer introducing a potential conflict to the recommendations (Oelke et al 2015).

There have been studies looking at the effectiveness of fesoterodine in patients that have previously failed to receive therapeutic benefit from other anticholinergic medications. Garcia-Baquero et al (2013) reported that fesoterodine was an optimal treatment option when previous clinical response to anticholinergics had been sub-optimal or not tolerated. However, in a review article by Morris & Wagg (2014) it was suggested that there was limited evidence to confirm the efficacy of fesoterodine in patients

with well-defined suboptimal response to all anticholinergics, however it appears to have a role in patients with insufficient response to tolterodine.

Chapple et al (2015) performed a systematic review of the clinical efficacy and safety of fesoterodine in the treatment of OAB in relation to patient profiles and confirmed that there is now extensive evidence to demonstrate the safety and efficacy of fesoterodine in relieving OAB symptoms in patients with various clinical and demographic profiles including the elderly and vulnerable patients.

In 2017, Heesakers et al published a review of the evidence for fesoterodine in the management of complex OAB patients. They described three complex groups of patients:

1. Women who have specific risk factors and conditions

2. Patients at risk of cognitive impairment who may have comorbidities, take multiple medications, or show Blood Brain Barrier deterioration

3. Elderly patients who are frequently frail and vulnerable and should be treated with caution

They reported that fesoterodine 4 mg and 8 mg have been studied extensively in these three patient groups, and has been shown to have pharmacological properties that confer clear clinical advantages. The review concluded that fesoterodine is efficacious, irrespective of sex or age, is well tolerated in older and vulnerable patients, and does not cause impairment in cognitive function.

Fesoterodine and Sexual Function

In all the literature reviewed, there were no trials identified that considered SF as a primary outcome and no trials using fesoterodine that assessed women with a validated SF questionnaire pre and post treatment. Many of

the phase 3 trials eg FACT 1 and 2, used QoL outcome measures that did not have SF or personal relationship domains so there are very few data. The SAFINA study did use the KHQ and overall in the study there was a change in the personal relationships domain of -16.1 points, suggesting an improvement in symptoms. However, when this change is viewed in comparison to the other domains, this is the second lowest change post treatment with only general health perception ranking lower. Therefore, further research into this aspect is needed.

Adverse effects

The most common side effects are related to the antimuscarinic properties of fesoterodine and are dry mouth, dry eyes, constipation and dyspepsia. The commonest side effect occurring was a dry mouth. This is representative of all antimuscarinics. It was however generally perceived to be mild to moderate in severity and discontinuation due to it is 1% or less in clinical trials (Pfizer 2011). Weissbart et al (2016) found that in women with OAB who were taking fesoterodine, although dry mouth prevented them from restricting their fluid intake, it did not diminish the treatment efficacy. Clinical experience has shown that side effects seem to decrease with time, possibly because of the natural course of the disease, and because the patients adapt their treatment accordingly (Heesakers et al 2017).

Studies by Chapple et al (2007) and Nitti et al (2007) showed that there was no difference in vital signs such as heart rate and blood pressure measurements when taking fesoterodine. There were also no significant changes in the QT interval on the electrocardiogram. Table 12 shows pooled data from two phase III randomised controlled trials (RCTs) detailing the most common adverse events i.e. those occurring > 2% of subjects. Other adverse events include: nasopharyngitis, influenza, dry throat and nausea.

Table 5.1 Common adverse events

(PBO =placebo, TOL ER = tolterodine extended release, FESO = Fesoterodine)

Adverse Event, n (%)	**PBO (n=283)**	**TOL ER 4mg (n=290)**	**FESO 4mg (n=272)**	**FESO 8mg (n=287)**
Any adverse event	107 (38)	144(50)	135(50)	167(58)
Dry mouth	20 (7.1)	49(16.9)	59(21.7)	97(33.8)
Constipation	4(1.4)	8(2.8)	9(3.3)	13(4.5)
Headache	14(4.9)	14(4.8)	12(4.4)	7(2.4)
Dry eye	0	1(<1)	6(2.2)	12(4.2)
Dizziness	7(2.5)	4(1.4)	4(1.5)	3(1.0)
Other adverse events	16(15.7)	31(10.7)	22(8.1)	26(9.1)

A study to evaluate the short and long term effects of fesoterodine on the eye reported that it increased the pupil diameter and decreased the accommodation amplitudes of the eye, but did not significantly affect the intraocular pressure. These changes were not deemed to be clinically important and no patients developed visual disturbances in the study (Acar et al 2016).

A copy of the fesoterodine SMPC has been included in the Appendix.

Cost effectiveness

In the UK, fesoterodine is recommended as a second line pharmacological therapy for OAB and has similar monthly prescription costs to other branded options at the lower dose. However, as the monthly price is the same regardless of dose, for patients on the higher dose it is cheaper per month than other branded anticholinergics.

In Spain, two assessments of the cost effectiveness of fesoterodine have been performed. One assessing flexible dosing and the use of fesoterodine as a first line therapy for newly diagnosed OAB in clinical practice (Peral et al 2016) and one comparing the use and health economics of fesoterodine versus tolterodine or solifenacin as a first line therapy in primary care (Sicras-Minar 2013). When compared to other anticholinergics, fesoterodine was found to be a cost-saving therapy for the treatment of OAB. When considering dosing regimens, for women who had had their symptoms for less than one year, fast escalation straight to the 8mg dose at the time of review was found to be more cost effective than the traditional recommendations of dose escalation (ie 4-8weeks).

Conclusions

Fesoterodine has been shown to be an effective drug in the treatment of OAB in women based on a number of good quality studies discussed within this chapter. Throughout the range of studies that have been performed, it appears to be well tolerated, cost effective and it is versatile and can be used in many different clinical populations. However, as with all antimuscarinic medications, there are still problems with long term persistence.

There is a lack of knowledge regarding its impact on SF as this has only been observed as a secondary outcome and not with a validated sexual function measure and there is not adequate evidence to answer the research question posed at the end of chapter 4.

Chapter 6

Development of the Trial

Introduction

Following on from the review of the literature, securing a research grant and the development of a research question as described in the previous chapters, the next stage of this thesis was to plan the methodology for a clinical trial to try to answer the question –

'Does fesoterodine have any effect on the sexual function of women with OAB?'

Based on this question the null Hypothesis was as follows:

'Fesoterodine has no effect on sexual function in women complaining of overactive bladder syndrome'.

This chapter aims to discuss the process of the development of the clinical trial of investigational medicinal product (CTIMP) that was performed, providing the rationale for the primary and secondary endpoints chosen, justifying the tools used for data collection, sampling methods and the methodological and ethical issues that were considered during the planning stages. The final protocol adopted will be included in the appendices.

Initial trial decisions

When trying to answer a research question, it is important to adopt an appropriate, robust research methodology to ensure high quality, reliable and valid data are produced. RCT's are considered the gold standard for trial design, however, for this study there were several factors that made this design neither feasible nor justifiable. As part of the IIR grant awarded for this study, it was agreed that Pfizer would provide the fesoterodine medication for all women in the trial, however they were unable to provide a placebo version. Further enquiries at the clinical trials pharmacy revealed that if we were to consider a placebo arm it would have a significant cost implication for which the study budget would have been inadequate and also

there would be a time implication to develop a placebo tablet that would negatively impact upon proposed time lines. Secondly, it would considerably increase the number of women that needed to be recruited into the study making it unfeasible for a single centre setting within the proposed time lines. Finally, as fesoterodine was already a licensed treatment for OAB and its efficacy and tolerability had already been extensively evaluated, it was considered that it could be deemed unethical to withhold treatment from women when it could be provided as routine care. A randomised cross over study design was also considered so that comparisons between groups could still be made, yet the same issues as identified in the RCT meant that this was not feasible.

This combination of methodological, ethical and practical concerns led to the decision for this to be an open label, prospective cohort study where the women taking part would act as their own controls and comparisons would be made by assessing the change in outcomes from baseline, till the end of the trial (ie a before and after intervention study). However, it did mean that the study would not be able to assess the potential of a placebo effect compromising the internal validity of the study and meaning that we cannot be sure that any observed changes can be attributed to the intervention (in this case fesoterodine), and not to other possible causes.

In an ideal study, not only would there be a comparison group but both groups would be blinded to their treatment allocation. In this study, blinding does not take place as all patients will receive active treatment and their decision to dose escalate based on treatment efficacy and tolerability will be sought. It has been identified that subjective estimates of intervention effects are exaggerated by 7% in non-blinded studies compared with blinded studies (Wood et al 2008). This may be part of the placebo effect, or the subjects desire to' please their clinician' with good outcomes. In order to potentially detect if the results are exaggerated in this study, a combination of subjective and objective outcome measures will be utilised as discussed later under the primary and secondary outcomes and physiological measures of bladder

function will also be undertaken and compared to the patient's clinical symptoms.

According to Ho et al (2018), before and after intervention studies are susceptible to selection / assignment bias, and instrument / measurement bias. Whilst Setia (2016) reported that cohort studies are useful for investigating multiple outcomes, there are some limitations that need to be considered during the design stage as they can introduce bias due to loss to follow up, confounding factors, measurement errors in the tools selected, classification issues and the possibility that participation in the trial may alter the subject's behaviour. It is therefore essential that outcomes need to be well defined and measured similarly in all subjects and this will be dependent on the measures chosen and when they are completed. The outcome measures should include both objective and subjective measures and should be of a high quality and validated in the population under investigation to reduce measurement error. All patients should complete the same assessments at each time point in the study and all subject to rigorous assessment to ensure that they do fit the classification and the patient group under investigation. These issues were all considered within the discussions later in this chapter regarding timelines, outcome measures / endpoints and inclusion / exclusion criteria.

Setting the Primary Objective

In order to answer a question, research objectives must be set. Objectives are specific targets set in order to achieve the research aim. Endpoints divide research objectives into several parts and address each part separately. Based on the literature reported in previous chapters and the identification of a knowledge gap, it was decided that SF would be the main focus of this trial and it was set as the primary outcome. According to the clinical trials reported in Chapters 2-5, SF has previously only been investigated as a secondary outcome and to our knowledge this is the first trial to do so as a primary outcome. This would ensure that it was appropriately powered to answer the research question, as previous trials in

this area had either been powered according to their primary outcome, which was generally impact on OAB symptoms, or had not included a power calculation. This was important as an underpowered study may not be able to detect a difference between the groups and the study may turn out to be falsely negative leading to a type II error. This could account for the differences it outcomes in the trials discussed in Chapter 4.

Timeframe for the intervention

For many of the OAB studies discussed in Chapter 3 and the fesoterodine efficacy studies reported in Chapter 5, assessments were performed at baseline and again after 12 weeks. At this time point it is reported that improvement in symptoms / effects of medications have been noticed and compliance with treatment is 69-96% as reported in a systematic review by Sexton et al (2011). Any longer and the compliance rate significantly reduces (up to 72% dropout rate reported by Sexton et al 2011) and this increases bias to the study due to subjects dropping out or not attending follow up resulting in incomplete data sets. There were no guidelines or recommendations suggesting optimal timelines for studies of SF so in line with the previous OAB studies and compliance date, the timeline was set to measure outcomes at baseline and 12 weeks. The primary objective set was:-

'To assess the impact of flexible dose fesoterodine on SF in women with OAB after 12 weeks compared to baseline'

Primary Outcome tools selected

As reported in Chapters 2 and 3, there are two main types of tool available to assess SF. The first is a generic measure of SF and the second is a condition specific assessment of SF. It was considered that the strengths of a condition specific tool would be that it is more sensitive in the population under investigation. However, it was also considered that problems with SF may not only be related to a woman's bladder condition and that a generic

measure may also be useful to identify general SF concerns that were not necessarily related to bladder symptoms. At the time of study set up, none of the available tools had been validated in women with OAB therefore it was decided by the team to include two tools to measure the primary outcome, one generic and one condition specific.

An appraisal of available questionnaires was performed as part of the literature review (See Chapter 2 and 3) and the final choices for all the questionnaires used in this study were based on a set of criteria pre-determined by the team. These criteria were: the quality and length of the tool, clinical experience with its use, its accessibility and ease of scoring system.

Quality of the tool

At the time of developing the study, the 4th ICI Incontinence textbook (Abrams et al 2009) was consulted to determine the recommendations for questionnaires (based on assessments of reliability and validity described in chapter 2, p51). At the time of protocol development, there were no generic SF measures validated in women with OAB that had a grade A rating (as described in chapter 2). There were four measures that had a grade B rating, these were the female sexual function index (FSFI), the Derogatis sexual functioning inventory (DSFI), the Sexual Quality of Life – Female Questionnaire (SQoL-F) and the Brief Index of Sexual Functioning in Women (BISF-W). The questionnaire descriptions and rationale for rejection have been included in Table 6.1.

Table 6.1 Questionnaire descriptions and rationale for rejection

Questionnaire (ICI rating)	**Description**	**Rationale for Rejection / selection**
Derogatis Sexual Functioning Inventory (DSFI) (Grade B)	A self reported version of semi structured interviews designed to provide a multidimensional assessment of sexual function in men and women	Validated in community samples of men and women – no validation in women with FSD so may not be valid in this study population
Brief Index of Sexual Functioning in Women (BISF-W) (Grade B	Self administered questionnaire designed to assess current levels of female sexual functioning and satisfaction	Only validated in women seeking routine gynaecological care but not those with urinary symptoms so may not be valid in this population
Female Sexual Function Index (FSFI) (Grade B)	Self administered questionnaire assessing key dimensions of sexual function in women	Would have been acceptable for use
Sexual Quality of Life Questionnaire Female (SQoL-F) (Grade B)	Self administered questionnaire to assess the impact of FSD on a women's sexual quality of life and to evaluate the benefits of therapeutic intervention	Selected

The FSFI had been validated in a population of women with OAB and had an acceptable quality rating so may have been a suitable tool. The SQOL-F was developed and validated by Symonds et al (2007) to assess the impact of FSD on a woman's sexual quality of life. It consists of a set of 18 statements, each asking about thoughts and feelings that subjects may have about their sex life. The statements may be positive or negative. Subjects respond on a 6-point Likert scales ranging from completely agree to completely disagree. A higher score represents a better quality of life. The

development of this questionnaire was sponsored by Pfizer and the inclusion of this tool as one of the primary outcome measures was specifically requested by Pfizer when approving the grant. As it was one of the tools with a grade B rating from the ICI and the Rogers study (2008) discussed in chapter 5 had used this to assess outcomes, it allowed their data to be used to determine the power calculation for the study and it was included as a measure of the primary outcome instead of the FSFI.

For the condition specific questionnaire, there were three measures that had a grade A rating at that time. The first was the GRISS, the second was the PISQ and the third was the International Consultation on Incontinence Questionnaire – female lower urinary tract symptoms – sex (ICIQ-FLUTS-sex). These are listed in table 6.2 along with the reasons for rejection.

Table 6.2 Condition specific questionnaire descriptions and rationale for rejection

Questionnaire (ICI rating)	**Description**	**Rationale for rejection / selection**
Golombuck Rust Inventory of Sexual Satisfaction (GRISS) (Grade A)	A self administered questionnaire to evaluate both the quality of a heterosexual relationship and each partner's level of sexual functioning within that relationship	Assess' both the partners sexual functioning in a relationship and this trial is only considering the impact on the woman's SF
International Consultation on Incontinence Questionnaire – female Lower Urinary Tract Symptoms Sex (ICIQ-FLUTSsex) (Grade A)	Self administered questionnaire to assess sexual matters associated with urinary symptoms and related bother	Good Quality but lack of experience and potential delay to request use and scoring system
Pelvic Organ Prolapse / Urinary Incontinence Sexual Questionnaire (PISQ) (Grade A)	To assess sexual function after surgery in women with pelvic floor dysfunction	Short form version proven to reduce burden on patients whist maintaining reliability and validity
Pelvic Organ Prolapse / Urinary Incontinence Sexual Questionnaire short form (PISQ-12) (Grade A)	As above but a shortened version	Selected

The ICIQ-FLUTS-sex was developed to assess sexual matters associated with urinary symptoms and related bother. It consist of four items - pain/discomfort because of dry vagina, impact of urinary symptoms, pain with sexual intercourse and urine leakage with sexual intercourse. The PISQ was developed to assess SF in women with pelvic floor dysfunction before and after surgery. It is a 31 item questionnaire that is validated in women with both UI and POP. In 2007, Barber developed a short form of the questionnaire known as the PISQ-12. It is a self-administered questionnaire consisting of 12 items. The short form has been proven to demonstrate excellent correlation with the full version but reduces time and burden on the patients who are completing the questionnaire (Rogers et al 2003). A lower score represents better SF.

Clinical experience, accessibility and scoring systems

At the time of study development, it was not routine practice to use a tool assessing SF as part of a standard patient assessment. SF measures had only ever been used in other research studies and were always secondary outcomes.

The research team had prior experience using the PISQ-12 so it was readily available, and there was knowledge and experience of the scoring systems. There was no experience with the use of the ICIQ-FLUTS-sex and there would be a time delay to apply for the tool and scoring system. As both had a Grade A rating and neither had been specifically validated in women with OAB (only women with LUTS), it was decided to use the tool that was already accessible and the PISQ-12 was selected as the second measurement of the primary endpoint.

In summary, the final decision made was to include the SQoL-F as a generic and the the PISQ-12 as a condition specific measure of SF. The primary endpoint was then defined as:-

Change in item scores of the Pelvic Organ Prolapse and Urinary Incontinence Sexual Questionnaire – short form (PISQ-12) and the Sexual Quality of Life- Female questionnaire (SQOL-F) at week 12 relative to baseline

Selecting the Secondary Objectives

Chapter 3, presented the existing evidence that women with OAB have a poorer SF and it is presumed that this is due to the impact of their symptoms. Although the focus of this study was to assess the impact of fesoterodine on women's SF, it was hypothesised that treatment with fesoterodine should improve / reduce their OAB symptoms and this in turn will improve their SF. If SF outcomes were to change without any change in OAB symptoms then further investigation into the mechanisms for poor SF in women with OAB would have to be considered. It could also be hypothesised that the known adverse effects of fesoterodine in women such as constipation, dry mouth / eyes, somnolence could potentially negatively impact on SF. Therefore, discussions regarding the secondary outcomes focused on criteria that would not only determine the impact of treatment on OAB symptoms but also on the adverse effects that would potentially negatively affect the primary outcome. The secondary objectives therefore included bladder diary variables (to assess change in OAB symptoms), quality of life assessment (to assess the impact of medication and their general health on symptoms), adverse event reporting (to assess tolerability of the medication), assessment of bowel function (to determine the impact of one of the most common side effects of treatment that may impact upon the outcome) and pre and post UDS (to help with classification of patients and assess treatment response).

These secondary objectives can be summarised as assessing the effect of flexible dose fesoterodine on:

- *micturition frequency per 24 hours, nocturnal micturition's per 24 hours, urinary urgency incontinence episodes per 24 hours and urgency episodes per 24 hours after 12 weeks compared to baseline*
- *treatment satisfaction and HRQL measures at 12 weeks compared to baseline*
- *tolerability and compliance with therapy*
- *on bowel function*
- *on UDS variables*

Selecting the secondary outcome measures and endpoints

The secondary objectives above have been selected to assist in answering the research question as well as minimising sources of measurement bias and reduce confounding variables. An example of a confounding variable could be a change in volume of fluid intake over the course of the study. Although the subjects will not be actively attending bladder retraining during the course of the study, attendance in the department will expose them to information and leaflets on display providing advice on good bladder health. If the subjects take this on board and reduce their fluid intake this may account for changes in bladder diary variables rather than the effect of drug and can be assessed with the completion of pre and post intervention bladder diaries. To answer the research question in this study, a combination of objective (bladder diaries) and subjective tools (QoL assessment, goal achievement, bowel symptoms) are required along with physiological measurements of bladder function (subtracted cystometry). The tools or assessments employed are reported and justified below.

Bladder Diary

Bladder diaries are commonly used, recommended tools in the investigation and management of patients with LUTS (Lucas et al 2012). They can be completed as part of the initial assessment of women with LUTS and throughout routine care to assess the impact of treatment on their symptoms. They may also be used to aid in the diagnosis of certain conditions. At the time of study design, the diagnosis of urinary frequency and nocturia were set in relation to an abnormal number of voids as demonstrated on a bladder diary (ie more than 8 voids per 24 hours or more than 1 void at night as defined by Abrams et al 2002) therefore, bladder diary variables were not only used to assess and monitor but also to classify and confirm a diagnosis as part of the inclusion criteria.

It was decided that each subject would complete a bladder diary for 3 consecutive days immediately preceding each study visit to record details including the time and volume of every void, time and volume of fluid intake, the time the subject arose and went to bed and urgency was assessed using a validated scale. A three-day diary has been demonstrated to provide better accuracy and increased patient compliance and convenience compared to 5 or 7 day diaries (Dmochowshi et al 2005). This meant that the common symptoms of OAB (eg urgency, urgency urinary incontinence, frequency, and nocturia) could be objectively assessed and monitored as a secondary endpoint as well as forming part of the screening criteria and inclusion requirements.

The Patient Perception of Intensity of Urgency score (PPIUS) is a single item tool used to assess patient perception of urgency intensity in women with UUI. It is a valid and reliable tool in the assessment of urgency in women with and without urgency incontinence (Cartwright et al 2011). The subject rates their feeling of urgency associated with each micturition episode using the 5 point Likert scale that is set out on their bladder diary.

The diary utilised in this study was the one that is currently used as part of routine care. It has been developed over many years and the subjects all had experience in completing the diary. A copy of the diary can be found in the appendices. At the time of setting the trial up, there was no validated bladder diary in existence as it was not until 2014 that the ICIQ bladder diary was developed and validated as a robust measure (Bright et al 2014).

Summary of Bladder Diary endpoints selected

- *Change in mean number of micturitions per 24 hours at week 12 relative to baseline*
- *Change in mean number of nocturnal micturitions per 24 hours at week 12 relative to baseline in subjects with >0 episodes during the 3-day baseline diary period. (Nocturnal micturitions were defined as those occurring between the time the subject goes to bed with the intention of sleeping and the time she rises to start the next day)*
- *Percentage change in UUI episodes per 24 hours at week 12 relative to baseline in subjects with >0 UUI episodes during the 3-day baseline diary period*
- *Change in mean number of urgency episodes per 24 hours at week 12 relative to baseline. (Urgency episodes were defined as those with a Patient Perception of Intensity of Urgency Score (PPIUS) rating of ≥ 2 in the diary*
- *Percentage change in urgency episodes per 24 hours at week 12 relative to baseline*

Measurement of quality of life

Patient's symptoms and improvement following treatment provide subjective assessment whereas investigations provide an objective measure. However, neither of these represent the patient's perception of her condition nor its impact on her quality of life. Thus it is important to have meaningful measurements to evaluate what patients want and how well this can be

achieved following appropriate intervention. For the last 30 years there has been an increasing interest in health related QoL and patient reported outcomes. It is essential to use appropriate tools depending upon what is to be measured.

At the time of protocol development, the department was involved in recruiting patients for the SAFINA trial (Cardozo 2010), investigating flexible dose fesoterodine in men and women with OAB. To measure the outcomes under investigation in this study, the Patient Perception of Bladder Condition (PPBC) and the King's Health Questionnaire (KHQ) were used.

The PPBC is a self-administered, single item, validated questionnaire that is used to assess patient's subjective impression of their current urinary problems. It was originally developed by Coyne and Matze (2002) as a global assessment of bladder condition and is a recommended measure by the European Medicine Evaluation Association and has an A grading from the ICI.

The KHQ (also known as the ICIQ-LUTSquol) was developed by Kelleher et al (1997) and provides a HRQL assessment for those with urinary symptoms and measures associated bother. It is a self-administered disease specific questionnaire containing 21 questions that are scored in nine domains (general health perception, incontinence impact, role limitations, physical limitations, social limitations, personal relationships, emotions, sleep/energy, and severity of urinary symptoms). It is one of the most extensively validated and reliable questionnaires and has an A+ grading from the ICI.

As the study team had experience using these measures, they were readily available and they had been validated demonstrating robust measures in the patient population under investigation it was decided to include these as measures of the secondary outcome

Originally, when I was registered with the School of Nursing it was felt that the outcomes were too quantitative and that a mixed methods approach

would allow for further insights to be gained. It was requested by the academic supervisors at that time, that a mixed methods questionnaire should be added with the aim of investigating patient's goals from treatment. It was considered that this approach would allow for the subjects to consider their own personal goals from treatment and determine what is most important to them. This would enable us to gain further insights into the ways in which symptoms may impact on an individual's quality of life and how as clinicians we can individualise treatment for women. Although, the addition of a further questionnaire could potentially add burden to the subjects, it was deemed that the advantages of including this additional dimension to the study outweighed the disadvantages and that this would be a positive inclusion.

The SAFINA study had been the first trial in the UK to include the Self Assessment Goal Achievement Questionnaire (SAGA) as one of the outcomes. The SAGA questionnaire is a patient completed, physician reviewed tool to assess treatment goals and achievement of goals for subjects suffering from OAB and/or other LUTS (Brubaker et al 2011). It is comprised of two parts, the first questionnaire rates the importance to the subject of her treatment goals. It contains 9 fixed goals and a further 5 open ended goals. The follow up questionnaire asks the subject to rate the degree of achievement of the subjects goals set at the beginning of the treatment. There is also a one item measure relating to subjects rating the extent to which they have achieved all their goals set. It was designed in 2008 by Kopp et al and further validated by Khullar et al (2010) so it was not available when the ICI book was published in 2009. It currently has a grade B recommendation (Abrams et al 2017).

As part of the SAFINA study, the researcher was given the opportunity to lead on the qualitative analysis of the SAGA questionnaire and published the findings in 2016. This then allowed for the results of the population in this study to be compared to those from all over the UK to look for similarities and variations in patients goals within the two cohorts. This work is presented in Chapter 10.

The final endpoints assessing QoL and patient satisfaction / goal achievement were:-

Patient Perception of Bladder Condition (PPBC)

- *Change in PPBC at week 12 relative to baseline*

King's Health Questionnaire (KHQ)

- *Change in total score of each domain at week 12 relative to baseline*

Self Assessment Goal Achievement Questionnaire (SAGA)

- *Achievement of patient orientated goals at 12 weeks relative to baseline.*

Adverse events / treatment tolerability

It was decided that subjective assessment of adverse events through self-reporting at each visit would be the simplest way to assess side effects and the tolerability of the treatment. However, it would not adequately address the two main concerns related to the potential detrimental effects of medication on SF (ie the 'drying effect' as discussed in Chapter 3, and the impact of constipation). The primary outcomes do assess arousal and pain during sex which can potentially be used to investigate a drying effect if this is noted by women. However, it was decided to include a tool that could assess changes in bowel habit whilst on medication and the impact that this could have on QoL.

Assessment of bowel symptoms

One of the most common adverse effects associated with antimuscarininc treatment is that of constipation. This is not only uncomfortable for the

patient but can also cause a worsening of OAB symptoms. A tool to measure constipation and its impact on patients would allow for this adverse event to be evaluated. However, it was also acknowledged that many individuals report side effects from medications, but it is only when these worsen presenting symptoms or significantly impact upon patient's QoL that medication is discontinued. Therefore, we needed a tool that could assess changes in constipation over time and the impact that constipation may have on the individuals QoL. In order to identify the most suitable tool expert opinion was sought (Professor Christine Norton). The Patient Assessment of Constipation Quality of Life (PAC-QoL) questionnaire was recommended. The PAC-QOL was developed by Marquis et al (2005) to address the need for a standardised, patient-reported outcome measure to evaluate constipation over time. It is a self-administered questionnaire containing 28 items group into 4 subscales covering worries and concerns, physical discomfort, psychosocial discomfort and satisfaction. Responses are measured on a five point Likert scale.

Within the final design, there are a total of 6 questionnaires to be completed on two occasions during the study. This may have introduced an element of questionnaire fatigue or respondent burden described by Parahoo (2006) as the discomfort put on participants by making use of their effort and time in completing the questionnaires. The short versions of questionnaires have been utilised where available and valid to reduce the time taken to complete questionnaire and ease respondent burden. Having time at study visits dedicated to reviewing the questionnaires with the subjects hopefully reduced any non-answer error.

Patient Assessment of Constipation Quality of Life Questionnaire (PAC-QOL)

- *Change in total score of each domain at week 12 relative to baseline*

Subtracted Cystometry

There are a number of measures of physiological assessment of bladder function that have been used in clinical studies to assess the impact of antimuscarinic drugs on bladder function. Traditionally these investigated during phase 2 and 3 of the drugs trials process.

Subtracted cystometry measures the relationship between the detrusor pressure and bladder volume on filling and between the detrusor pressure and urine flow rate on voiding. During the procedure a pressure line and filling catheter are inserted into the bladder and a pressure line into the rectum (or vagina) and the bladder is filled with saline. Any changes of pressure in the bladder are recorded during this time. Once the bladder is full the patients are asked to perform a cough provocation test to assess for USI and provoked DO and other methods of provocation eg handwashing, star jumps may be performed to trigger symptoms. Finally patients void into a flowmeter to assess the pressure changes within their bladder and their flow rate as they void. As previously discussed in Chapter 3, all women presenting to the department with LUTS have this test performed as part of their routine investigation. Although this study will investigate women with OAB symptoms, a proportion of them will have been diagnosed as having DO on subtracted cystometry.

Originally, cystometry was not planned to be included as an outcome measure. However, when transferring this PhD from the School of Nursing to the School of Life Sciences, an additional objective measure was requested to compare outcomes in women with and without DO. This work had already been performed by Nitti et al (2009) who found that regardless of the presence of DO, patient's response to fesoterodine was dose proportional and independent of the UDS diagnosis. It was therefore suggested that the UDS could be used to assess if changes in SF were related to UDS variables or if it was independent of the UDS diagnosis. Due to the ethical considerations of performing additional tests, time and associated costs it was agreed that subtracted cystometry would be

performed at the end of treatment in a pilot group of women. The first forty subjects who consented to this additional assessment were included and the data from their test performed at initial assessment in the department was used to compare with the end of treatment data. The specific parameters in the bullets summarised below were chosen to reflect the expected effect of fesoterodine. Traditionally anticholinergics are thought to increase the first sensation of bladder filling, increase the cystometric capacity and reduce the amplitude or frequency of detrusor contractions, therefore these variables were set for investigation. However, as this study is for women with OAB, only a percentage of them with have DO hence the need to assess and then subgroup analyses can be performed if appropriate.
The summary of UDS parameters to be included are:-

- *Change in first sensation of filling / desire to void*
- *Change in maximum cystometric capacity*
- *Change in time to first detrusor contraction*
- *Presence of DO*

Inclusion Criteria

To ensure that the subjects had the characteristics that matched the study population under investigation and prevent classification error, stringent inclusion criteria were set. These needed to ensure that the women had OAB symptoms and were sexually active. In order to define OAB, the inclusion criteria from other clinical trials for antimuscarinics were reviewed. In all the big studies eg STAR trail (Chapple et al 2005), SUNRISE Trial (Cardozo et al 2008), FACT studies (Herschorn et al 2010a, Kaplan et al 2011), SAFINA study etc OAB inclusion criteria was not only based on the ICS definition but had included a requirement of a frequency of micturition of 8 or more voids in a 24 hour period, at least three episodes of urgency per 24 hours on a three day diary assessed using a validated urgency scale and evidence that the symptoms have been present for at least three months. To be able to compete the bladder diaries, the subjects had to be able to and

willing to complete the diaries and be able to read and write in English. The SAFINA trial inclusion criteria covered all of these and they were deemed relevant to this study so it was decided to copy these (Inclusion criteria 1-4 and 5-7 below. The only missing criterion was related to sexual activity.

When this protocol was developed the definition of SA was poorly defined in the literature and there were no recommendation on how to ask. Women were asked if they were SA, and the woman made her own interpretation of what that entailed and either responded yes or no. It was considered that adding a criterion to just confirm that the subject was sexually active could present uncertainty into the study as it did not determine a frequency of SA. Given that the intervention and plan of assessments were time bound, we needed to ensure that the subjects had been SA regularly during the time period to have noticed a potential change in SF. If we did not define or quantify SA, there would be the potential that women who may identify themselves as SA, were enrolled in the study but not be SA within the course of the study providing unreliable post intervention assessments. The challenge with defining SA was a lack of literature regarding 'normal' frequency of SA or variations of this with age and a lack evidence to suggest how many times it is appropriate to be SA with the time frame for any change in SF to be recognised.

After many discussions with supervisors and lack of comparable studies to review their criteria, it was set that a mean frequency of once per week was the minimum level of SA (Criterion 5 below).

Summary of Inclusion Criteria

Subjects must have met all of the following inclusion criteria to be eligible for enrolment into the trial.

1. *Female outpatients aged 18 – 80 years*
2. *Overactive bladder symptoms (subject reported) for ≥ 3 months prior to screening visit according to ICS guidelines*

3. Mean urinary frequency of ≥ 8 micturitions per 24 hours as verified by the screening bladder diary prior to baseline / Visit 2

4. Mean number of Urgency episodes ≥ 3 per 24 hours as verified by the screening bladder diary prior to baseline / Visit 2

5. Sexually active with a mean frequency of sexual activity ≥ 1 per week.

6. Able and willing to complete the micturition bladder diaries and all trial related questionnaires, comply with scheduled clinic visits and clinical trial procedures

7. Capability of understanding and having signed the informed consent form after full discussion of the treatment and its risks and benefits

Exclusion Criteria

Exclusion criteria are a set of predefined definitions that is used to identify subjects who will not be included or who will have to withdraw from a research study after being included. Exclusion criteria are guided by the scientific objective of the study and have important implications for the scientific rigor of a study as well as for assurance of ethical principles (Salkind 2010). Inclusion and exclusion criteria are meant to provide justification of subject appropriateness for the study, to minimise withdrawal (loss to follow up) and ensure that primary end-points of the study are reached.

The exclusion criteria set in the SAFINA study ensured that all the confounding variables that could introduce bias to the outcome of the study and could impact upon the effect of fesoterodine were ruled out. These included allergy to the drug (Criterion 1), concomitant medications (discussed later and criterion 11), along with identifying other medical problems that may be the underlying cause of OAB symptoms or may exacerbate symptoms including, UTI's, bladder pain, long term catheter use, previous incontinence surgery, current pelvic malignancy or previous radiotherapy in the area (Criteria 3-7, 9-10, 15). Contraindications or safety concerns including pregnancy and breastfeeding or history of drug / alcohol abuse or participation in another clinical trial were interactions were unknown

were included (criteria 11-14) . As these were readily available and had already been used in practice to recruit women they were adopted for this study.

It was noted, that the exclusion criteria did not sufficiently cover other urogynaecological problems that may impact upon SF so criteria were added to ensure that women with a significant prolapse were excluded (Criterion 2). Although women with mixed urinary incontinence would be screened for inclusion in the trial, it was decided that the urgency / OAB needed to be their predominant symptoms, therefore those with stress predominant MUI were also added as an exclusion (Criterion 8). An exclusion criteria was also set to leave out subjects not complying with follow-up visits (Criterion 17). It was hoped that this comprehensive and extensive list of exclusion criteria would reduce the potential bias from confounding factors, loss to follow up and ensure that patients are correctly classified prior to enrolment in the study.

Summary of Exclusion Criteria

Subjects presenting with any of the following were not included in the trial.

1. Any condition that would contraindicate the use of fesoterodine including, but not limited to: hyposensitivity to the active substance (fesoterodine fumarate) or any of the excipients, or to peanut or soya; urinary retention; gastric retention; uncontrolled narrow angle glaucoma; myasthenia gravis; moderate or severe hepatic impairment (Child Pugh C); severe renal impairment; severe ulcerative colitis; and toxic megacolon

2. Stage 3 or greater pelvic organ prolapse, defined as tissue protruding to or beyond the introitus in lithotomy position at rest (without increase in intra-abdominal pressure)

3. History of lower urinary tract surgery (eg. Incontinence surgery, diverticulectomy, OTIS urethrotomy) with the exception of any minor surgery (eg. Cystoscopic procedures)

4. A known history of interstitial cystitis or a significant pain component associated with OAB symptoms, uninvestigated haematuria, urogenital cancer, interstitial or external radiation to the pelvis or external genitalia, or bladder outlet obstruction, radiation cystitis, genito-urinary tuberculosis, bladder calculi, urethral obstruction or detrusor-sphincter dysenergia

5. Subjects with bladder stones. Subjects with a previous history of bladder stones may be included

6. Previous history of acute urinary retention requiring catheterisation, clinically relevant bladder outlet obstruction or severe voiding difficulties in the judgement of the investigator prior to Visit 2 (baseline)

7. Use of an indwelling or an intermittent self-catheterisation programme

8. Symptoms of incontinence being predominantly stress urinary incontinence as determined by the investigator

9. Urinary tract infection (UTI) as shown by the results of the urinalysis at screening or recurrent urinary tract infections (RUTIs) defined as treatment for UTI ≥3 times in the last year

10. Use of any electrostimulation, bladder training, or pelvic floor exercises (with certified incontinence practitioners) within 4 weeks prior to Visit 1 (Screening)

11. Participated in any clinical trial or received an investigation drug within 4 weeks prior to Visit 2

12. History of alcohol abuse and /or any other drug in the opinion of the investigator

13. Subjects who were pregnant, nursing, or who intended to become pregnant during the trial or within three months after the completion of the trial

14. Subjects of childbearing potential who are heterosexually active but not using an adequate form of contraception. Reliable contraception methods were defined as hormonal methods of contraception (including oral,

patches, injected, implants, IUDs, condom with spermicidal foam/gel/film/cream/suppository, tubal ligation or male partner who has had a vasectomy for a least 4 months)

15. Subjects who had any medical (including known history of major haematological, renal, cardiovascular or hepatic abnormalities) or psychological condition or social circumstances that would impair their ability to participate reliably in the trial, or those who may increase the risk to themselves or others by participating

16. Had any current malignancy except

a. Those ≥5 years ago without recurrence

b. Excised basal cell skin carcinoma or squamous cell cancer

17. Subjects who, in the opinion of the investigator, were not likely to complete the trial for any reason

Concomitant medication

A confounding factor that can introduce bias into a study is the effect of concomitant medication. If a subject is already taking a drug that may impact upon OAB symptoms (either positively or negatively) these need to be identified and ruled out (either by stopping treatment for the trial or if this is not possible then screen failing the subject). Criteria 1 and 2 recognise other drugs that may be used to treat OAB and criterion 3 details the drugs that may worsen symptoms.

Drug interactions are possible whenever medication is ingested. During phase 1 and 2 of the clinical trials process many of these interactions will be identified and warnings put in place to recommend that the drugs (or drug and food substance) are not taken in conjunction with each other as they may potentiate or reduce the effect / or metabolism / or excretion of the drug. This may introduce a bias into the study, therefore criteria 4-6 were set in line with the manufacturers and BNF recommendations.

Summary of Concomitant medications

All medications with the exceptions of those listed below were permitted concurrently with the study medication. If a subject needed to start one of the excluded medications during the study she was withdrawn.

1. *Treatment with antimuscarinic OAB medication within 2 weeks prior to Visit 2 (baseline), including any preparation containing: darifenacin, oxybutynin, propiverine, tolterodine, fesoterodine, solifenacin and trospium. If any of these preparations were started during the study the patient would be withdrawn*
2. *Initiation of treatment during the 12 week trial period with:*
   a. *Any other drug treatment for OAB including all the antimuscarinics listed in point 1 and mirabegron*
   b. *Any drugs with significant anticholinergic, antispasmodic, parasympathetic, or cholinergic agonistic effects*
3. *Intermittent or unstable use of diuretics or alpha blockers, or tricyclic antidepressants, oestrogen therapy and any 5AR inhibitors or initiation of such treatment(s) within 2 weeks prior to Visit 2 (baseline) or during the study*
4. *Treatment with moderate or potent CYP3A4 inhibitors, such as grapefruit juice, macrolide antibiotics (erythromycin, clarithromycin), immunosuppressants (cyclosporine), azole antifungal agents (ketonazole, itraconazole), protease inhibitors within 3 weeks prior to Visit 2 (baseline), or the expectation to start such a treatment during the trial*
5. *Administration of medication capable of inducing hepatic enzyme metabolism or transport (eg. rifampicin, carbamazepine, phenobarbital, phenytoin, or St John's Wort) at any point during the study or within the 6 weeks prior to Visit 2 (baseline)*
6. *Treatment with potent CYP2D6 inhibitors such as bupropion, cinacalcet, fluoxetine, paroxetine or quinine at any point during the study*

Plan of Assessment - Investigations

As part of the screening assessment, it was recognised that basic investigations would be required to ensure that women meet the inclusion / exclusion criteria, the rationale for each test performed is discussed below.

Urine dipstick analysis

Urinary tract infection (UTI) may cause or exacerbate urinary symptoms and in line with the ICS / IUGA definition of OAB must be excluded (Haylen et al 2010). If a subject had a UTI it may negatively affect the outcomes of the study therefore a dipstick urinalysis was taken from all women at the screening visit or if they attended for an unscheduled visit. A mid-stream urine sample was sent for culture and sensitivities in all suspected UTI's and enrolment delayed until the subject was infection free.

Urine Pregnancy test

Pregnancy and breastfeeding are listed as exclusion criteria for this study as the effect of fesoterodine on these is unknown. Therefore prior to starting medication, potential pregnancy needs to be ruled out. For such an important concern, patient reporting is not enough and an objective measure is needed to confirm that the patient is not pregnant. At the screening visit all women of childbearing potential had a urine pregnancy test performed to ensure that they were not pregnant prior to starting medication.

Post void residual (PVR)

Incomplete bladder emptying can be associated with an increased risk of UTI and worsen urgency and frequency hence the presence of a significant PVR may negatively impact on the outcome of this study as incomplete bladder emptying can cause symptoms of OAB. Urinary retention is also a risk associated with fesoterodine. Following micturition an assessment of bladder emptying was undertaken using an either a bladder scanner or in

and out catheter in line with the departmental policy. A significant PVR was set as 100ml or greater and if subjects were found to have a significant PVR they were managed in line with departmental policy but deemed ineligible for this study.

Dosing Regimen

As with routine clinical practice, normal dosing of fesoterodine starts at 4mg once daily for four weeks and can then be escalated to 8mg once daily if clinically indicated and tolerated. This is known as flexible dosing. It was decided therefore that this should form the basis of the timeline where all women would be started on 4mg once daily and then after four weeks given the option to stay on the same dose or escalate to 8mg. In many clinical trials cited earlier in Chapter 4 assessing the efficacy of fesoterdine, the final assessment was performed after 12 weeks of therapy. To keep in line with other studies it was decided that this would be the point of reassessment for this trial and whichever, dose of medication the patient chose at week 4 would be continued until week 12. This choice of 4 or 8 weeks for treatment should also aid the dispensing of medication as commercial stock comes in packs of 28 tablets.

Sample Size

This study aimed to investigate change in SF, using the SQOL-F and the PISQ-12 as measures of SF at baseline and 12 weeks after intervention. Sample size calculations were performed by the study statistician. Prior data by Rogers et al (2008) indicated that a difference in the response to SQOL-F (Primary outcome) of matched pairs is normally distributed with standard deviation 19.2 and a difference in the mean response of 6.4. These estimates were used to calculate the sample size using 95% power, and a two sided alpha level of 0.05. The number of participants required to detect the difference described at the significance level described, was 120 patients. Allowing for a 10% dropout the number set for recruitment was 132 women.

Pilot study

According to Leon et al (2011) a pilot study can be used to evaluate the feasibility of recruitment, randomisation, retention, assessment procedures, new methods, and implementation of novel interventions. Although a pilot study would have been beneficial to ensure that the study design was appropriate, the department has had a lot of clinical trial experience with anticholinergic drugs at Phase 2, 3 and 4. The research design reflected the experience that had been gained and methodological issues identified in previous trials had helped to inform this study design. These included strict adherence to specific inclusion / exclusion criteria and the use of short forms of questionnaires where available to minimise responder burden.

Feasibility / Timetable

For a single centre study, recruiting 132 patients could be considered quite ambitious. However, the department had a flow of about 180 new patients a month. Of these, approximately half (90 women) reported OAB symptoms and about two thirds (60 women) of these would start medication for their symptoms. All of these patients were offered the opportunity to participate in the trial if they meet the inclusion / exclusion criteria. It was planned that 10 patients would be recruited per month over a 15 month period. Long standing patients would also be recruited from the nurse led and outpatient clinics when they attend for medication reviews. It was planned that the 15 month period would allow for an attrition rate of approximately 20%, however, recruitment could be terminated early once 132 patients had completed the trial. The study site was and still is active in many areas of research, however, during the time plan for this study there were not any other trials investigating patients with OAB.

Ethical Issues Considered

As this was a CTIMP, all practice adhered to the standards set by the Good Clinical Practice in Research Trials (ICH 1997). Good clinical practice is a set of internationally recognised ethical and scientific quality requirements which must be observed for designing, conducting, recording and reporting clinical trials that involve the participation of human subjects. It was also registered with the Medicines and Healthcare products Regulatory Agency (MHRA). All trial personnel completed training courses in these principals.

Patient counselling and future considerations

Patients were provided with an information sheet about the purpose of the trial, what they could expect from the trial and what was required of them (A copy of the patient information sheet (PIS) has been included in the appendix). Women had the opportunity to further discuss any questions or concerns with the investigator before providing informed consent for participation (the informed consent form can be found in the appendices). Current best practice in trial development includes patient involvement to ensure that protocols are feasible, all trial information is appropriate and easy to understand, however, this protocol was developed in 2010 before this was embedded in practice. In this study there was no patient involvement in the original development of the PIS, but the ethics committee lay members suggested some changes to the language that were made as part of the ethical approval process.

There may have been implications with the sample as they were from the investigators clinical setting and there was a risk that some people may feel that their medical or nursing care may have been negatively affected if they did not agree to be research subjects (Burns & Grove 2003). To reduce this effect, participants were informed that if they did not enter the trial or if they withdrew from the trial at any point, that it would not affect the standard of care that they received from the department.

As the effect of fesoterodine on SF was unknown, it reduced the influence the investigator had over the patients when counselling them with regarding participation and hopefully further reduced any effect of coercion.

This was a particularly sensitive area to discuss with patients; however, all patients seen in the department were asked about their SF on initial assessment so it did not require a change in routine practice or introduce any additional embarrassment or invasion of privacy for the patients considering participation in the trial.

Another area that was considered was regarding what services could be offered to patients if they continue to complain of sexual dysfunction on completion of the trial. The standard department procedure following treatment for their bladder condition is onward referral for psycho-sexual counselling. This was offered to the subjects at the final visit if they remained symptomatic.

Industry involvement

The study was funded through an IIR Grant from Pfizer LTD who manufactured fesoterodine. However, they had no involvement with the design of the trial (except the use of the SQOL-F), data collection or data analysis. Also they are not in a position to withhold the results should the findings be negative. Over the course of this thesis, the marketing and commercial sales of fesoterodine has been taken over by a different pharmaceutical company - Pierre Fabre but this has not had any implications for this study.

Patient beneficence and reimbursement

As participation in the trial entailed two additional visits to the department over routine care this may have placed a financial burden on the patient. To compensate for this, patients were offered reimbursement for their travel costs up to £20 per visit on receipt of a valid train ticket or car park voucher.

Participants were also given the option of where they would like to complete the questionnaires. They had the option to take them home to complete at their leisure or offered a private room in the department. For those subjects who agreed to have the additional subtracted cystometry at visit 4, they were reimbursed £50 for the additional time and discomfort.

It was hoped that this study would prove to be worthwhile for the participants as they would receive a treatment that could provide a solution or resolution to their problems with few limitations (2 extra visits) whilst also providing beneficence for the wider good when the final data have been analysed.

Conclusions

This chapter describes and justifies the methods used in this CTIMP of fesoterodine. The following chapter will go on to describe the trial implementation, amendments and analysis.

Chapter 7

Trial implementation, processes and analysis

Introduction

Based upon the decisions discussed in Chapter 6, the first complete CTIMP protocol was developed in 2010 and titled:-

‘A 12 week, single centre, open label study to evaluate the effect of fesoterodine flexible dosing regimen on the sexual function of women with overactive bladder.’

This full protocol is included in the appendix. The protocol was reviewed and authorised with the relevant bodies. This chapter details some of the final decisions not previously discussed in relation to drug administration, dispensing, assessment of compliance and the final plan of trial activities. It will also detail the changes to the trial as it progressed and the significant issues with recruitment that led to an increase in study sites, a review of the inclusion criteria and amendments to the protocol. Finally a detailed plan of the statistical analysis of the trial is described prior to the presentation of the results in Chapter 8.

Trial Medication – Investigational Medicinal Product (IMP)

Fesoterodine fumarate is an antimuscarinic agent that was developed and licensed for the treatment of the symptoms that may occur in patients with OAB syndrome. It is manufactured and supplied by Pfizer Ltd (Now Pierre Fabre in Europe).

The study drug was supplied in bottles with two different strengths as described below (see Table 7.1 For description of IMP):

Fesoterodine fumarate prolonged release 4mg tablets

Fesoterodine fumarate prolonged release 8mg tablets

Table 7.1 Description of IMP

Product name	**Colour**	**Strength**	**Dosage form**	**Package form**	**Route of administration**
Fesoterodine fumarate	Light blue	4mg	Prolonged release tablet	Clinical trial Bottles	Oral
Fesoterodine fumarate	blue	8mg	Prolonged release tablet	Clinical trial Bottles	Oral

Dosing Regimen

The study drug was dispensed according to the following schedule:

Visit 1 – screening – no medications dispensed

Visit 2 (Week 0) – one bottle (28 tabs) of 4mg tablets

Visit 3 (Week 4) –One bottle (56 tabs) of 4mg tablets or one bottle (56 tabs) of 8mg tablets, depending on the dose selection for each individual subject at this visit (based upon a discussion between the subject and the investigator of the efficacy and tolerability reported by the subject, the investigator either increased the dose to 8mg for those subjects who desired greater symptom improvement and reported good tolerability, or continued the subject on the 4mg dose for the remaining 8 weeks of the study).

No dose adjustments were allowed after visit 3 during the last eight weeks of the treatment phase. Subjects were advised to take one tablet with water at approximately the same time every day and that it should be swallowed whole without chewing. Fesoterodine could be administered with or without food.

Drug Accountability

CTIMPS are subject to regulatory processes that needs to be adhered to eg those set by the MHRA and the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) principles. These are set to protect the safety, well being and right of subjects in clinical trials. Drug accountability is one particular area where specific requirements were essential and the details of how we adhered to this are noted below.

All IMP supplies were stored in accordance with applicable regulatory requirements. IMP was stored separately from normal hospital stocks. Until dispensed to the subjects all IMP was stored in a securely locked area, only accessible to authorised personnel.

The investigator was responsible for recording the receipt, administration and return of all trial medication, and for ensuring the supervision (via the hospital pharmacy) of the storage and allocation of trial medication. A complete inventory was performed of the trial medication upon delivery to the site.

Overall IMP accountability logs were completed during the trial. The subjects were asked to return all trial medication bottles, whether full, partially full or empty, to the investigator and the investigator retained these bottles at the site until accountability had been completed. Compliance was agreed as taking at least 80% of the expected IMP. At the end of the trial excess IMP was destroyed and adequately documented.

Sponsorship

An investigator initiated unrestricted research grant was awarded by Pfizer to cover pharmacy costs, patient expenses and administration of the trial. All relevant regulatory approvals were gained and are discussed later in this chapter.

As this was a pharmaceutical trial the Principal Investigator (PI) needed to be a medical doctor or a qualified nurse prescriber, educated to at least master's level. As I did not meet these requirements at the start of the study, the Professor of the department assumed the role of PI and I was the Chief Investigator.

The Study was sponsored by the Joint Clinical Trials Office (JCTO) and they were responsible for the monitoring and auditing of trial practices and conduct.

Plan of Assessment

This was designed as a single centre open label prospective observational study which aimed to enter 132 SA female subjects with OAB symptoms. The study was carried out at the Urogynaecology department at KCH, London. Convenience sampling was used to recruit patients to this study from UDS clinics, the nurse led service and general outpatient clinics. Due to challenges with recruitment with this study three additional study sites were set up to recruit and this will be discussed later in the chapter.

Trial Procedures

A trial activities log was developed to show all the assessments and investigations that took place at each visit and this is displayed in figure 7.1.

To ensure that all required data were captured and to assist with monitoring of the trial a paper clinical research form (CRF) was developed, along with an informed consent form, patient information leaflet and GP letter, in line with the sponsors specifications. These are all included as appendices.

Figure 7.1 Trial Activities Log

Protocol Activity	**Visit 1** **Screening** **-14 days** **(±7days)**	**Visit 2** **Baseline** **Week 0**	**Visit 3** **Escalation** **Week 4** **(±7days)**	**Visit 4** **End of TX** **Week 12** **(±7days)**	**Telephone Follow up** **Week 24**
Written informed consent	X				
Demographics & History	X				
Physical exam	X				
Inclusion / exclusion criteria	X	X			
Body mass index (BMI)	X				
Urine dipstick test and PVR	X				
Urine pregnancy test	X			X	
Menopausal status	X			X	
PISQ-12		X		X	
SQoL		X		X	
PPBC		X		X	
KHQ		X		X	
PAC-QoL		X		X	
SAGA		X		X	
Dispense 3 day bladder diary	X	X	X		
Evaluation of bladder diary		X	X	X	
Adverse events		X	X	X	x
Concomitant medication	X	X	X	X	
Dose assessment and titration			X		
Dispense study medication		X	X		
Study medication return			X	X	
Subtracted cystometry				X	
Assess drug compliance			X	X	x
Assess treatment continuation					x

Initial Contact

A range of recruitment methods were used including the use of posters and flyers in clinical areas, waiting rooms and in the toilets. Women attending appointments within the department eg for bladder retraining and medication reviews were sent a leaflet with appointment letters and the new women referred in to the department for urodynamics were also sent flyers. Women identified in the urodynamcis, main outpatient and nurse led clinics were provided with a PIS and for those who had contacted the department having seen a poster, they received a PIS by either post or email dependent on their individual preferences. All women provided with a PIS were contacted 48 hours later (by phone or email) by the investigator to see if they were interested in taking part in the study and to arrange a screening visit.

If the subject agreed to take part in this study, a date for a screening visit was set, at which point written consent was taken and the following tests were carried out to determine whether they were eligible to take part in this study.

Visit 1 (Screening visit)

At the screening visit:

- Weight, medical history (including any medication and non-drug treatment) and demography taken
- Sitting blood pressure and pulse taken
- A physical examination conducted by a HCP
- Subjects provided a sample of urine for the following-:
    - A urine dipstick test performed to exclude blood and infection
    - A urine pregnancy test for women of child bearing potential performed
- Subjects issued with a 3-day bladder diary to complete and provided with instructions on how and when to complete the diary. The diary was to be completed for the three (3) days prior to the next visit

If subjects meet all of the study entry requirements at this point and they agree to participate in the study, they were invited to return for Visit 2 (baseline visit).

A patient card was provided to the subjects to act as an appointment reminder which also included emergency contact details of the research team.

Visit 2 (Week 0) (Baseline)

At this visit, following assessment of eligibility by a delegated HCP, subjects were informed whether they were eligible to take part in this study. If they were eligible and still wished to participate, a baseline visit was performed.

At the baseline visit-:

- A completed bladder diary was collected and evaluated
- Subjects were asked to complete 6 questionnaires which took approximately 30 minutes (These could completed at home and returned if preferred)
- Subjects were asked if they have had any new symptoms or worsening of existing symptoms and if they have taken any new medication or treatments since the last visit.
- Subjects were given another 3-day diary (plus instructions) to complete the three days prior to the next visit (visit 3)
- Subjects were given a supply of IMP (fesoterodine 4mg) to take once a day at approximately the same time each day over the next 4 weeks

Visit 3 (Week 4)

Four (4) weeks later subjects returned for visit 3.
During this visit:

- A completed bladder diary was collected and evaluated
- Subjects were asked if they have had any new symptoms or worsening of existing symptoms and if they have taken any new medication or treatments since their last visit

- The investigator reviewed the amount of unused study medication subjects had returned to assess compliance
- Subjects were given another 3-day diary (plus instructions) to complete the three days prior to the next visit (visit 4)
- The dose of IMP was reviewed by the study team and if required the dose increased and recorded in notes and CRF
- Subjects were given a supply of IMP, either fesoterodine 4 mg or fesoterodine 8 mg depending on discussions with the investigator

Visit 4 (Week 12 End of Treatment or Early Termination Visit)

Eight (8) weeks later subjects returned for visit 4.
During this visit:

- A completed bladder diary was collected and evaluated
- Women of child bearing potential provided a sample of urine for a pregnancy test
- Subjects were asked to complete questionnaires which took approximately 30 minutes (These could be completed at home prior to the visit if preferred)
- Subjects were asked if they had any new symptoms or worsening of existing symptoms and if they have taken any new medication or treatments since their last visit
- The investigator reviewed the amount of unused study medication subjects have returned to assess compliance
- For those women who had consented to having urodynamics they underwent subtracted cystometry at this visit. (This was only for the first 40 subjects in the trial who consent to having subtracted cystometry performed at week 12)

Telephone Follow UP (24 Weeks)

- Subjects were asked if they were still taking fesoterodine (as prescribed by their GP) or if they were taking any other anticholinergic

medication or no therapy

- If subjects had decided to stop all therapy they were asked to explain their decision for this
- Subjects were asked if they had experienced any adverse events on completion of the trial

Protocol deviations

In the Urogynaecology unit at KCH the majority of women reporting LUTS complete a 3 day bladder diary and undergo video UDS as part of their routine care. If the subject had received information related to the trial prior to this routine care (to meet GCP consent requirements) the screening visit and visit 2 were performed concurrently and the bladder diary that they completed as part of routine care was accepted.

Statistical Analysis

Primary outcomes

The primary outcomes variables in this study were looking for the difference between the PISQ-12 total score and the SQoL-F total score over the course of the study. The mean difference in questionnaire scores between week 0 and 12 was analysed using dependent T-tests. This test measures the difference in mean score between two related groups.

Secondary outcomes

Dependent T-test were completed for the KHQ, and Pac-QoL (As the “How Satisfied” domain was scored on an ascending scale, while the others were scored on a descending scale, the inverse of this domain score was used in all analyses) and examined differences within individual domains, as well as the overall scores.

Dependent T-tests were also used to examine changes in PPBC score and urodynamic parameters between weeks 0 and 12.

Descriptive statistics were used to analyse and compare bladder diary variables.

Effect size was calculated using Hedge's *g,* as it is less prone to upward bias in sample sizes under 20 when compared with other measures such as Cohen's *d*. To further reduce the overestimation of effect sizes among this small sample, a correction factor was applied (Hedges and Olkin 1985).

The relationship between UDS parameters and the baseline total scores for each questionnaire were examined using multinomial regression analyses. These were also used to examine any association between changes in UDS parameters with changes in total score for each questionnaire. All urodynamic parameters were entered as covariates in the models via a forced entry method. The goodness-of-fit of the resulting models was determined using the F-ratio.

For the SAGA questionnaire, a non-parametric rank correlation analysis was used to examine the relationship between the perceived importance of a patient's self-determined goals and the attainment of that goal. Kendall's tau statistic was reported as this is more accurate than Spearman's rho when using small sample sizes. All analyses were completed using IBM SPSS 22 (for Mac).

Table 7.2 describes all the statistical abbreviations used in the text and the tables in all the results chapters in this thesis.

Table 7.2 Statistical abbreviations

Statistical abbreviations	Description
$\bar{x}$	Symbol for the mean
SE	The standard error around each coefficient
BCa	Bias-corrected and accelerated – the method of bootstrapping used
Df	The degree of freedom
$t_{(19)}$	Symbol for the t-test (DF in brackets)
P	The probability value
g	Hedge's g – a measure of effect size
Sig	The statistical significance of the test
Wald	Wald test – used to determine whether each predictor variable affects the outcome variable
B	Unstandardized beta - equation coefficient for each predictor variable
SE *B*	Standard error for the unstandardized beta
β	The standardised beta
t	The t-test statistic calculated for the individual predictor variables
VIF	Variance Inflation Factor – measure of validity of regression model
$\chi^2(2)$	Symbol for the chi-square test (DF in brackets)
Exp(B)	Odds ratio in logistic regression
R^2	Coefficient of determination in regression analysis to assess goodness of fit
F ratio	Used to determine if there are differences between groups
Tolerence	An indicator of multicollinearity in multiple regression

Amendments to the study

This project experienced many delays and challenges along the way which resulted in multiple amendments and several protocol changes. From the time of funding approval in April 2010, ethical approval was not gained until June 2012 and the first subject was not enrolled into the study until October 2012 due to a delay in getting IMP on site. Recruitment to the study proved difficult and despite changes to the inclusion criteria, the addition of three external research sites and one patient identification centre and an active recruitment period over four years until 31st December 2016, only a fifth of the sample size was met. Table 7. 3 details the problems that were identified, the amendments made to the protocols to address the issue and the associated protocol numbers.

Table 7.3 Amendments to the protocol

Problem identified	**Amendments**	**Associated protocol**
Inclusion criterion for frequency of SA negatively impacting upon recruitment	Changes to the inclusion criterion in line with new literature regarding frequency of SA	2.5
Lack of women being recruited to the study	Study changed from single centre to multi centre by addition of one patient identification centre and three research sites	2.1-2.4
Inclusion criterion for urinary frequency / 24 hours negatively impacting upon recruitment	Changes to the inclusion criterion in line with new ICS / IUGA definitions	2.5
Study due to end without opportunity for new criteria to improve recruitment	Extension to study time lines	2.6
Pfizer unable to provide clinical research supply of fesoterodine	Commercial stock provided for subjects	2.0

In view of the amendments summarised above there have been many minor and substantial amendments submitted to the REC and R&D and multiple versions of the research protocol as it has been updated. Lists of all the regulatory submissions over the course of the study and details all of the protocol versions and dates for this study along with a brief description of the changes applied have been included in the appendix. A full discussion relating to these problems will be addressed in Chapter 9.

Conclusions

This chapter has described the processes that were involved for each of the participants who enrolled into the trial, the plans for statistical analysis and the major changes and amendments that were made to the study protocol. The next chapter will present the quantitative findings from the study.

Chapter 8

Quantitative Results

Introduction

This chapter will report the findings of the CTIMP previously outlined in chapter 7. Following the description of the subject disposition and baseline characteristics, the results of all the primary and secondary outcomes will be presented. The discussions and analysis of the results will be reported in Chapter 9.

Recruitment by Site

All recruits into the trial were from the initial study site. Two of the additional sites did not manage to recruit any subjects. The third additional site did manage to successfully screen and identify one subject. When the subject was due to start treatment, however, there had been a temperature violation in the storage of IMP in the pharmacy department and all the stock had to be destroyed. The subject did not want to wait for a new supply to be delivered to the site so decided to withdraw and start an alternative treatment. This subject has not been included in the analysis in this chapter.

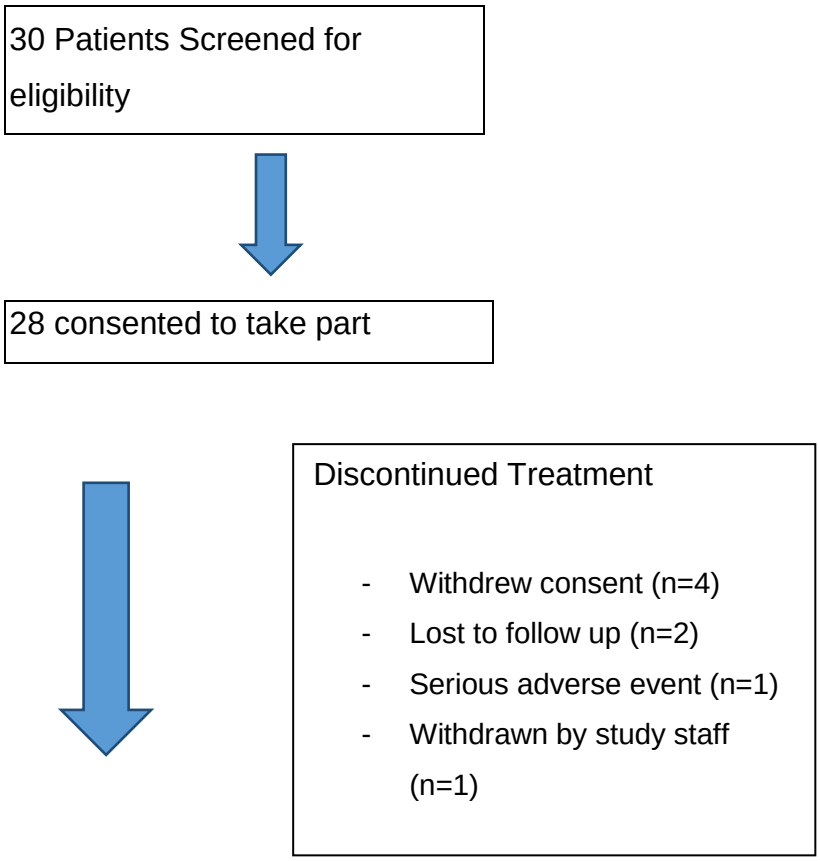
Subject Disposition

Thirty subjects were screened, 28 were allocated to treatment of which 20 completed treatment. The screen failures were due to one patient failing eligibility on her bladder diary variables (prior to the protocol change) and the other had just been started on a contraindicated medication so did not meet the inclusion criteria.

Of the eight subjects who discontinued treatment, four withdrew consent (one prior to starting treatment decided she no longer wanted to try another medication so did not collect her prescription, one because she wanted to start a family and therefore would not use the necessary contraception, one as her relationship status changed and she was no longer sexually active, one as she was starting a new job and felt she could not commit to the trial procedures). Two subjects were lost to follow up at the 12 week stage (one

did make contact to say that she was not available to attend and then failed to attend three further appointments, one moved out of the area and could not return to complete trial procedures). One subject was withdrawn from the trial as she was not complying with trial procedures. The final subject was removed from the trial due to a serious adverse event (SAE). Despite a negative pregnancy test on the initiation of treatment, when the subject returned for the week four visit she reported that she had not yet had a period since the last visit. A pregnancy test was performed and was positive and the subject was withdrawn from the study and an SAE declared. Complete data sets are available for 19 subjects as one did not complete her final bladder diary. The flow of subjects through the study is demonstrated in figure 8.1.

Figure 8.1 Subject Flow Chart



Baseline Demographics and Clinical Characteristics

The median age of subjects in the trial was 40 years with a median BMI of 29 and median parity of 2. The median length of time that OAB symptoms had been present was 1 years with a range of 3 months – 25 years and only one patient in the study was treatment naive in relation to antimuscarinic therapy (all other subjects having received at least first line therapy from their GP prior to referral to the department). 60.7% were Caucasian and 35.7% post-menopausal.

When considering the clinical characteristics, 64.3% had DO on UDS, 81.5% reported UI (2 subjects with OAB were found to have mild USI but the OAB was their most bothersome problem). Overall, 53.7% of subjects opted to dose escalate during the study. When dose escalation was broken down according to UDS diagnosis and patients who withdrew from the study prior to dose escalation were removed, 75% of subjects with OAB opted to dose escalate compared to 60% of those with DO. This is demonstrated in table 8.1.

Table 8.1 Baseline demographics and clinical characteristics

Demographic	**Median**	**Range**	**95% Confidence Intervals**
Age	40 years	20-73 years	37 - 47.2
BMI	29	21-44	26.7 - 31
Parity	2	0-6	0.847 – 2.07
OAB symptoms	1 years	0.25-25 years	1.99 – 5.91
Menopausal Status			
Pre menopause		64.3%	
Post menopause		35.7%	
Ethnicity			
Caucasian		60.7%	
Black		32.2%	
Asian		7.1%	
Baseline diagnosis			
OAB		35.7%	
DO		64.3%	
Incontinence Status			
No		18.5%	
Yes		81.5%	
Dose Escalation			
No (n=8)		28.7%	
Yes (n=15)		53.7%	
N/A (n=5)		17.6%	
Diagnosis	**Dose escalated**		**Non escalated**
OAB (n=8)	75%		25%
DO (n=15)	60%		40%

Primary Outcome

PISQ-12

Paired T-Test PISQ-12 Total Score

Of the 20 subjects tested, the average PISQ-12 score decreased between week 0 ($\bar{x}$ =15.85, SE =1.74) and week 12 ($\bar{x}$ = 11.5, SE = 1.52). This difference of 4.35 points, BCa 95% CIs [7.35, 1.572], was statistically significant $t_{(19)}$ = 3.159, p = 0.005, and reflects a moderate effect size, g = 0.542.

Table 8.2 Demonstrates the breakdown for each question on the PISQ-12 and the mean score at week 0 and week 12.

Figure 8.2 Displays the change in PISQ-12 domain scores between week 0 and week 12.

Overall there was mean reduction in PISQ-12 score of 4.35 which was significant (p=0.005). When considering specific questions related to desire, there was very little change in the frequency of sexual desire, the number of orgasms experienced or whether women feel “turned on”. However, by week 12 there was a significant improvement in satisfaction with the variety of sexual activities in the women’s sex lives.

When looking into the effect of study medication on SA there is an observed reduction in the frequency of CI (mean difference -0.5) but this is just short of significant (p=0.056) (see table 8.3) and there is no change in the number of patients who never experience CI, yet there is a significant reduction in the restriction of sexual activity caused by fear of incontinence (mean -0.75 p=0.004) (see table 8.4).

Table 8.2 The paired t-tests for individual PISQ-12 domains and overall PISQ-12 scores from week 0 to week 12.

PISQ Questions	Mean at week 0 (SE)	Mean at week 12 (SE)	Paired Differences					
			Mean difference	BCa 95% Confidence Interval of the Difference		t	df	Sig. (2-tailed)
				Lower	Upper			
PISQ 1	1.75 (0.16)	1.7 (0.11)	0.050	-0.200	0.350	0.326	19	0.748
PISQ 2	1.7(0.26)	1.6 (0.29)	0.100	-0.250	0.450	0.623	19	0.541
PISQ 3	0.85 (0.18)	0.85 (0.17)	0.000	-0.350	0.350	0.000	19	1.000
PISQ 4	1.35 (0.2)	0.8 (0.23)	0.550	0.200	0.850	2.604	19	0.017
PISQ 5	1.9 (0.25)	1.25 (0.25)	0.650	0.250	1.102	2.557	19	0.019
PISQ 6	1.5 (0.3)	1.0 (0.22)	0.500	0.150	0.950	2.032	19	0.056
PISQ 7	1.65 (0.34)	0.9 (0.26)	0.750	0.300	1.300	3.290	19	0.004
PISQ 8	0.8 (0.3)	0.45 (0.22)	0.350	0.000[b]	0.800[b]	1.505	19	0.149
PISQ 9	1.15 (0.34)	0.55 (0.21)	0.600	0.100	1.200	2.108	19	0.049
PISQ 10	0.3 (0.15)	0.3 (0.15)	0.000	-0.300[c,d]	0.300[c]	0.000	19	1.000
PISQ 11	0.4 (0.17)	0.2 (0.12)	0.200	0.000[e]	0.450[e]	1.285	19	0.214
PISQ 12	2.5 (0.19)	1.9 (0.22)	0.600	0.250	1.050	2.349	19	0.030
PISQ Total Score	15.85 (1.74)	11.5 (1.52)	4.350	1.900	7.030	3.159	19	0.005

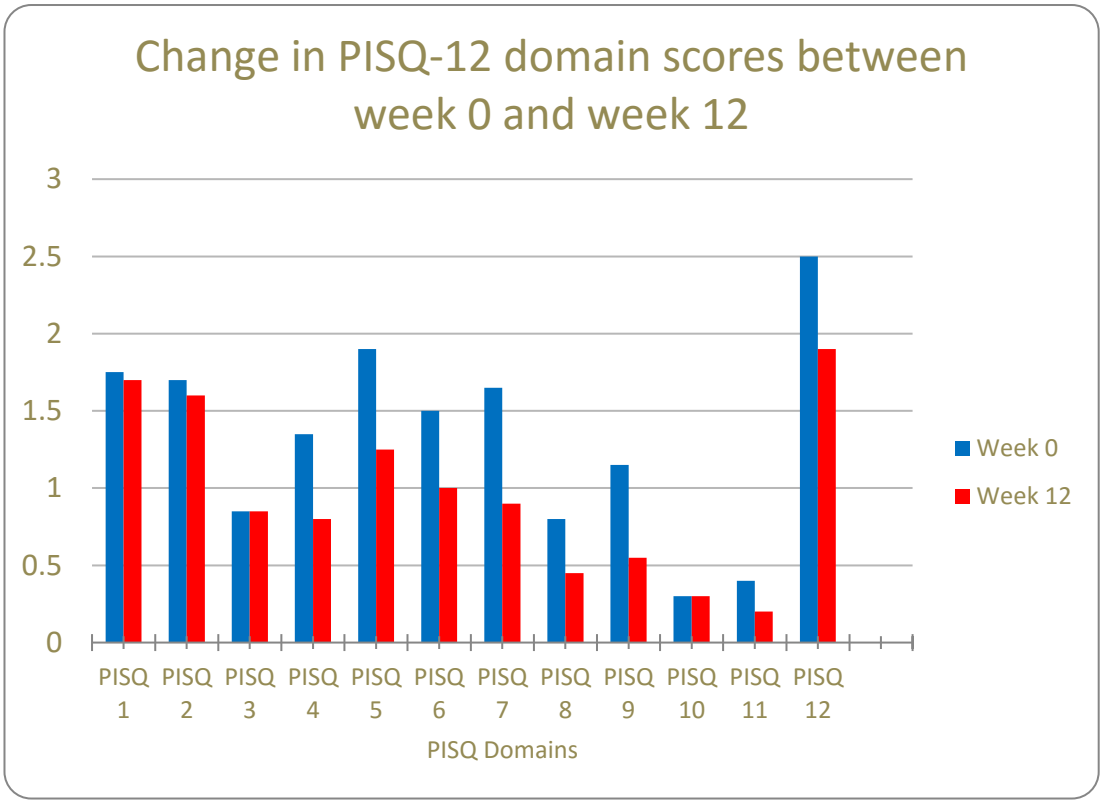
Table 8.3 Are you incontinent of urine with sexual activity?

PISQ-12 Question 6	**No of patients at Week 0**	**No of patients at Week 12**
Always	3	1
Usually	0	0
Sometimes	7	3
Seldom	4	10
Never	6	6

Table 8.4 Does fear of incontinence restrict your sexual activity?

PISQ-12 Question 7	**No of patients at Week 0**	**No of patients at Week 12**
Always	4	1
Usually	1	1
Sometimes	6	3
Seldom	2	4
Never	7	10

Figure 8.2


Change in PISQ-12 domain scores between week 0 and week 12
3
2.5
2
1.5
1
0.5
0
PISQ 1
PISQ 2
PISQ 3
PISQ 4
PISQ 5
PISQ 6
PISQ 7
PISQ 8
PISQ 9
PISQ 10
PISQ 11
PISQ 12
PISQ Domains
Week 0
Week 12

SQOL-F

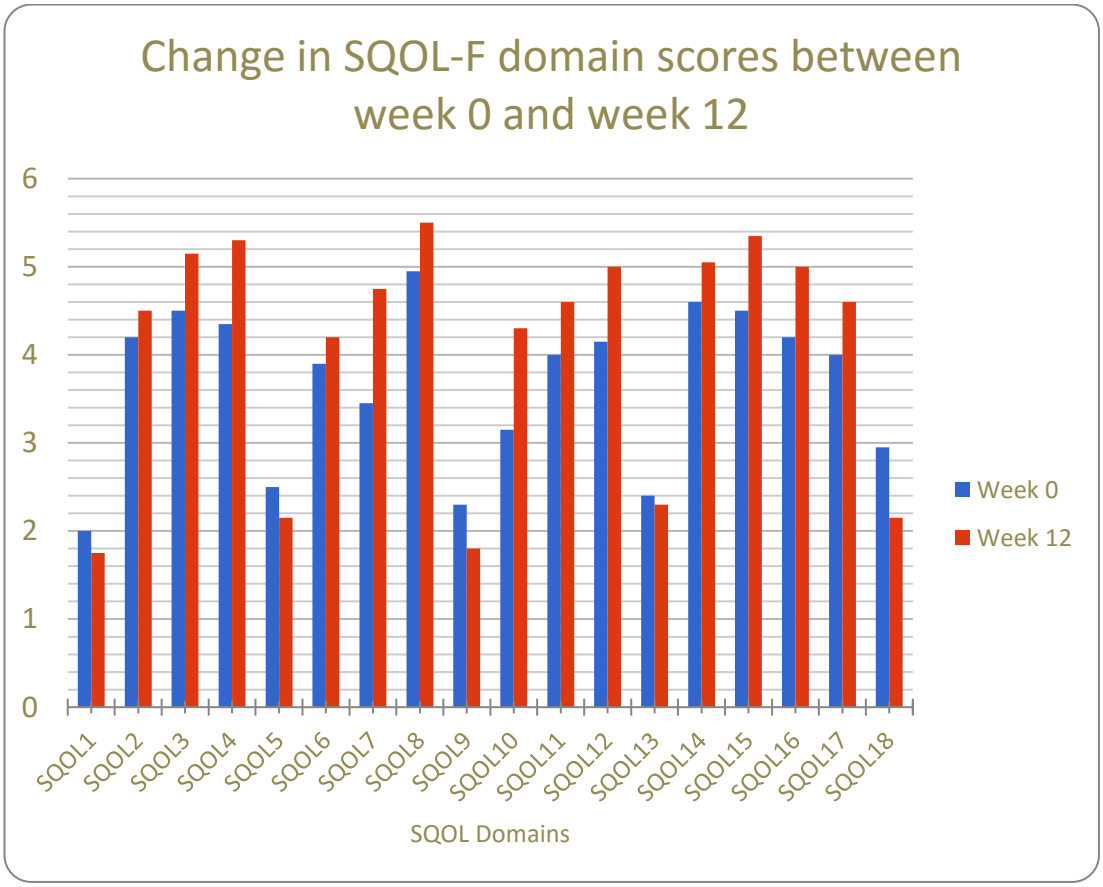
Paired T-Test SQOL-F Total Score

Of the 20 subjects tested, the average SQOL score increased between week 0 ($\bar{x}$ = 66.1, SE = 3.62) and week 12 ($\bar{x}$ = 73.45, SE = 2.42). This difference of 7.35 points, BCa 95% CIs [-2.55, -13], was statistically significant $t_{(19)}$ = -2.673, p = 0.015, and reflects a moderate effect size, g = -0.486.

Table 8.5 displays the mean change for each of the 18 questions on the SQOL-F from week 0 to 12.

Figure 8.3 demonstrates the mean change in SQOL-F scores between week 0 and week 12.

Figure 8.3



	Mean at week 0 (with SE reported in brackets)	Mean at week 12 (with SE reported in brackets)	Paired Differences						
			Mean difference	BCa 95% Confidence Interval of the Difference		t	Df	Sig. (2-tailed)	Effect Size (corrected Hedge's g)
				Lower	Upper				
SQOL1	2 (0.251)	1.75 (0.28)	-.250	-.200	.700	-.960	19	.349	0.191
SQOL2	4.2 (0.374)	4.5 (0.336)	.300	-.950	.200	.922	19	.368	-0.171
SQOL3	4.5 (0.394)	5.15 (0.31)	.650	-1.250	-.150	2.292	19	.033	-0.372
SQOL4	4.35 (0.443)	5.3 (0.309)	.950	-1.550	-.400	2.826	19	.011	-0.506
SQOL5	2.5 (0.267)	2.15 (0.274)	-.350	.050	.650	-1.926	19	.069	0.263
SQOL6	3.9 (0.397)	4.2 (0.408)	.300	-1.100	.400	.825	19	.419	-0.152
SQOL7	3.45 (0.4)	4.75 (0.354)	1.300	-1.950	-.700	3.577	19	.002	-0.751
SQOL8	4.95 (0.4)	5.5 (0.295)	.550	-1.100[b]	-.150[b]	1.993	19	.061	-0.318
SQOL9	2.3 (0.356)	1.8 (0.268)	-.500	-.036	1.150	-1.602	19	.126	0.323
SQOL10	3.15 (0.393)	4.3 (0.43)	1.150	-1.750	-.600	3.092	19	.006	-0.568
SQOL11	4 (0.503)	4.6 (0.373)	.600	-1.400	.200	1.390	19	.181	-0.275
SQOL12	4.15 (0.449)	5 (0.324)	.850	-1.650	-.050	2.031	19	.056	-0.441
SQOL13	2.4 (0.336)	2.3 (0.356)	-.100	-.550	.650	-.335	19	.741	0.059
SQOL14	4.6 (0.413)	5.05 (0.312)	.450	-1.100	.250	1.280	19	.216	-0.250
SQOL15	4.5 (0.444)	5.35 (0.335)	.850	-1.600	-.200	2.165	19	.043	-0.439
SQOL16	4.2 (0.462)	5 (0.348)	.800	-1.600	.000	1.823	19	.084	-0.397
SQOL17	4 (0.47)	4.6 (0.387)	.600	-1.400	.200	1.352	19	.192	-0.283
SQOL18	2.95 (0.426)	2.15 (0.357)	-.800	-.250	-1.500	-2.320	19	.032	0.413
SQOL Total	66.1 (3.615)	73.45 (2.416)	7.35	13	2.55	2.673	19	.015	0.191

Table 8.5 Mean change for SQOL-F from week 0 to 12

Secondary Outcomes

Bladder diary variables

Complete bladder diaries were available for 17 subjects. Paired T-Tests were performed to establish differences in bladder diary variables from week 0 to week 12.

Number of episodes of micturition per 24hrs

The average number of episodes of micturition per 24 hrs decreased between week 0 ($\bar{x}$ = 10.05, SE = 0.63) and week 12 ($\bar{x}$ = 6.95, SE = 0.72). This difference of 3.11 episodes, BCa 95% CIs [1.98, 4.26], was statistically significant $t_{(16)} = 4.839$, $p < 0.001$, and reflects a large effect size, $g = 0.993$.

Number of Episodes of nocturia per 24hrs

The average number of episodes of nocturia per 24hrs decreased between week 0 ($\bar{x}$ = 0.82, SE = 0.12) and week 12 ($\bar{x}$ = 0.32, SE = 0.10). This difference of 0.51 points, BCa 95% CIs [0.26, 0.75], was statistically significant $t_{(16)} = 4.441$, $p < 0.001$, and reflects a large effect size, $g = 0.973$.

Number of Episodes of UUI per 24hrs

The average number of episodes of UUI per 24hrs decreased between week 0 ($\bar{x}$ = 1.68, SE = 0.43) and week 12 ($\bar{x}$ = 0.65, SE = 0.45). This difference of 1.02 points, BCa 95% CIs [0.49, 1.59], was statistically significant $t_{(16)} = 3.096$, $p = 0.007$, and reflects a moderate effect size, $g = 0.502$. This represents a 61.3% reduction in UUI episodes per week.

Number of Episodes of U per 24hrs

The average number of episodes of U per day decreased between week 0 ($\bar{x}$ = 4.65, SE = 0.55) and week 12 ($\bar{x}$ = 1.31, SE = 0.38). This difference of 3.34

points, BCa 95% CIs [2.38, 4.39], was statistically significant $t_{(16)} = -5.95$, $p = 0.00$, and reflects a large effect size, $g = 1.524$.

Number of Episodes of U per 3 day diary

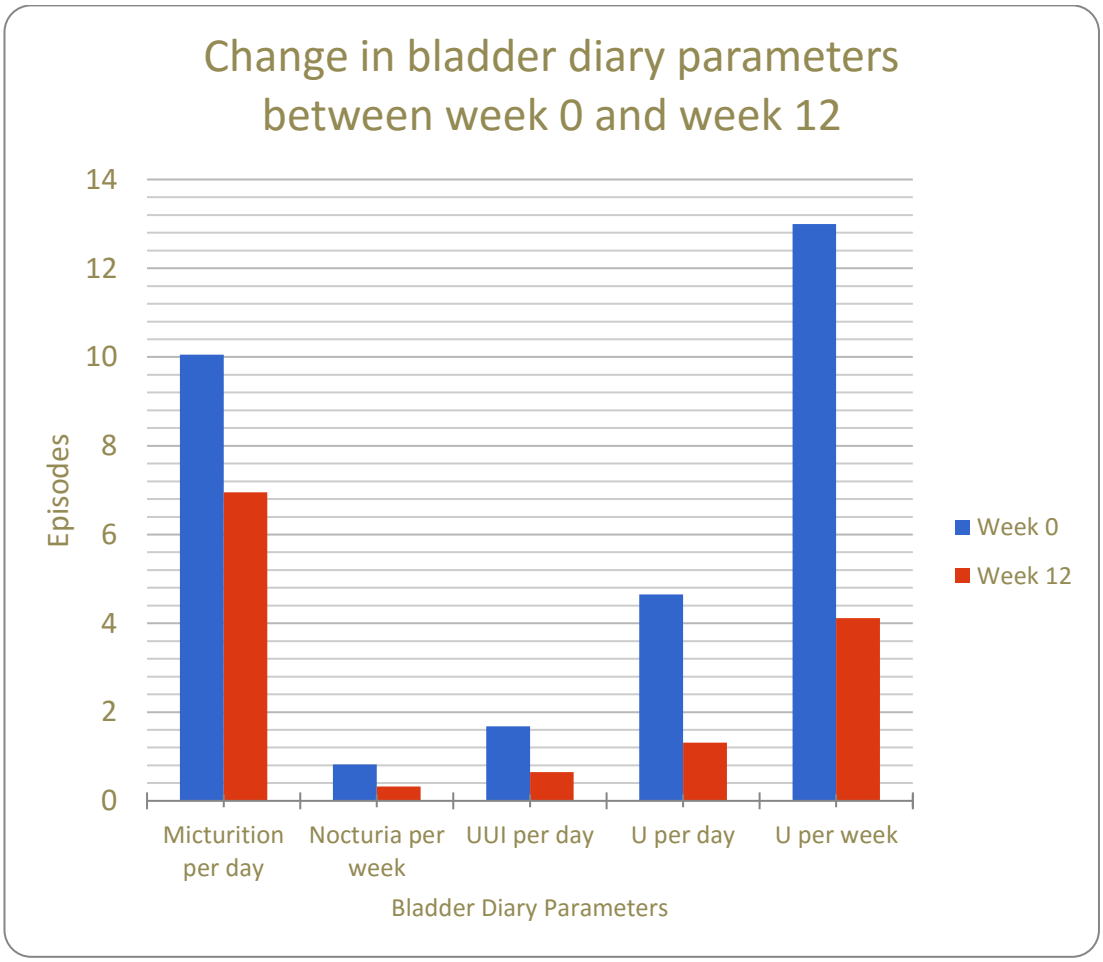
The average number of episodes of U per week decreased between week 0 ($\bar{x} = 13$, SE = 1.4) and week 12 ($\bar{x} = 4.12$, SE = 1.13). This difference of 8.88 episodes, BCa 95% CIs [6.14, 11.5], was statistically significant $t_{(16)} = 6.862$, $p < 0.001$, and reflects a large effect size, $g = 1.51$. This represents a 68.3% reduction in urgency episodes per week.

24 hour Fluid Intake Volumes

The average 24 hour fluid intake decreased from 1507mls at week 0 to 1246mls at week 12 (t=2.545, p value=0.021). This is a significant finding and equivalent to an 18% reduction in total fluid intake over the course of the study. The average 24 hour fluid output decreased from 1576mls at week 0 to 1355mls at week 12 (t=1.922, p value=0.072). However, this did not quite reach significance.

Table 8.6 shows the mean change in bladder diary variables from week 0 to 12. Figure 8.4 demonstrate the changes in bladder diary parameters between week 0 and week 12.

Figure 8.4


Change in bladder diary parameters between week 0 and week 12
14
12
10
8
6
4
2
0
Episodes
Micturition per day
Nocturia per week
UUI per day
U per day
U per week
Bladder Diary Parameters
Week 0
Week 12

Bladder Diary	Mean at week 0 (with SE reported in brackets)	Mean at week 12 (with SE reported in brackets)	Paired Differences						Effect Size (corrected Hedge's g)
			Mean difference	BCa 95% Confidence Interval of the Difference		t	df	Sig. (2-tailed)	
				Lower	Upper				
Number of Episodes of micturition per day	10.05 (0.63)	6.95 (0.72)	3.11	1.98	4.26	4.839	16	0.000	0.993
Number of Episodes of nocturia per day	0.82 (0.12)	0.32 (0.10)	0.51	0.26	0.75	4.441	16	0.000	0.973
Number of Episodes of UUI per day	1.68 (0.43)	0.65 (0.45)	1.02	0.49	1.59	3.096	16	0.007	0.502
Number of Episodes of U per day	4.65 (0.56)	1.31 (0.38)	3.34	2.38	4.39	5.95	16	0.000	1.524
Number of Episodes of U per week	13 (1.40)	4.12 (1.13)	8.88	6.14	11.50	6.862	16	0.000	1.510

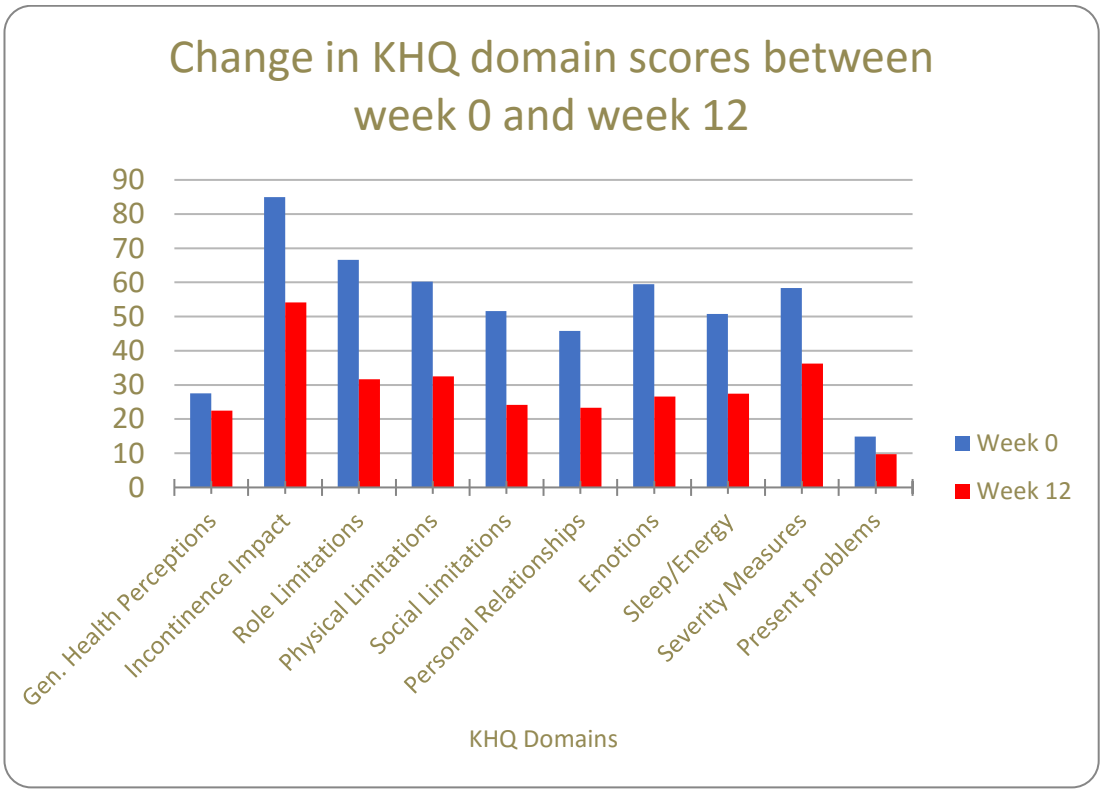
Table 8.6 Mean change in bladder diary variables

KHQ

Paired T-Test King's Health Questionnaire (KHQ) Total Score

Of the 20 subjects tested, the average KHQ score decreased between week 0 ($\bar{x}$ = 520.18, SE = 40.2) and week 12 ($\bar{x}$ = 288.21, SE = 43.48). This difference of 231.97 points, BCa 95% CIs [302.41, 164.64], was statistically significant $t_{(19)}$ = 6.892, p <0.001, and reflects a large effect size, g = 1.126.
There were significant changes in every domain of the KHQ with the greatest changes observed in role limitations, emotions and incontinence impact domains (mean difference of 35.01, 32.8, 30.84 respectively) (see table 8.7). The least change was seen in the general health perception and present problems domains (mean difference 5.0 and 5.15 respectively). Figure 8.5 demonstrates the change in KHQ domain scores.

Figure 8.5



KHQ Domains	Mean at week 0 (SE)	Mean at week 12 (SE)	Paired Differences					
			Mean difference	BCa 95% Confidence Interval of the Difference		t	df	Sig. (2-tailed)
				Lower	Upper			
KHQ1 General Health Perceptions	27.5 (5.71)	22.5 (5.41)	5.0000	2.5000[b]	8.7500[b]	2.179	19	0.042
KHQ2 Incontinence Impact	84.98 (4.51)	54.14 (7.12)	30.8350	18.3302	44.5580	5.434	19	0.000
KHQ3 Role Limitations	66.64 (6.05)	31.63 (6.39)	35.0050	23.3308	46.6746	5.688	19	0.000
KHQ4 Physical Limitations	60.23 (6.09)	32.46 (6.67)	27.7700	14.4426	40.8666	3.906	19	0.001
KHQ5 Social Limitations	51.65 (6.93)	24.15 (6.99)	27.5000	15.8200	39.1725	4.205	19	0.000
KHQ6 Personal Relationships	45.8 (7.73)	23.32 (7.29)	22.4900	6.6650	39.9897	2.862	19	0.010
KHQ7 Emotions	59.44 (6.16)	26.64 (5.66)	32.7950	23.9450	41.1158	7.188	19	0.000
KHQ8 Sleep/Energy	50.8 (6.34)	27.46 (5.71)	23.3450	12.5349	35.8300	3.909	19	0.001
KHQ9 Severity Measures	58.31 (5.41)	36.23 (5.74)	22.0800	17.0750	27.0838	8.110	19	0.000
KHQ Present problems	14.85 (1.03)	9.7 (1.2)	5.1500	3.5503	6.8500	7.054	19	0.000
KHQ Total Score	520.18 (40.2)	288.21 (43.48)	231.9700	170.4986	297.2971	6.892	19	0.000

a. Unless otherwise noted, bootstrap results are based on 1000 bootstrap samples

b. Based on 991 samples

Table 8.7 Mean change in KHQ

PAC-QOL

Paired T-Test PAC-QOL Total Score

Of the 20 subjects, the average PACQOL score decreased between week 0 ($\bar{x}$ = 28.25, SE = 5.57) and week 12 ($\bar{x}$ = 25.6, SE = 4.5). This difference of 2.65 points, BCa 95% CIs [8.97, -3.65], was not statistically significant $t_{(19)} = 0.716$, $p = 0.483$, it reflects a small effect size, $g = 0.106$.
There were no significant differences noted in any domain of the PAC-QOL questionnaire as demonstrated in table 8.8 and Figure 8.6

Only one subject reported constipation as an adverse effect and for majority the IMP had no impact on their daily bowel habits.

Figure 8.6

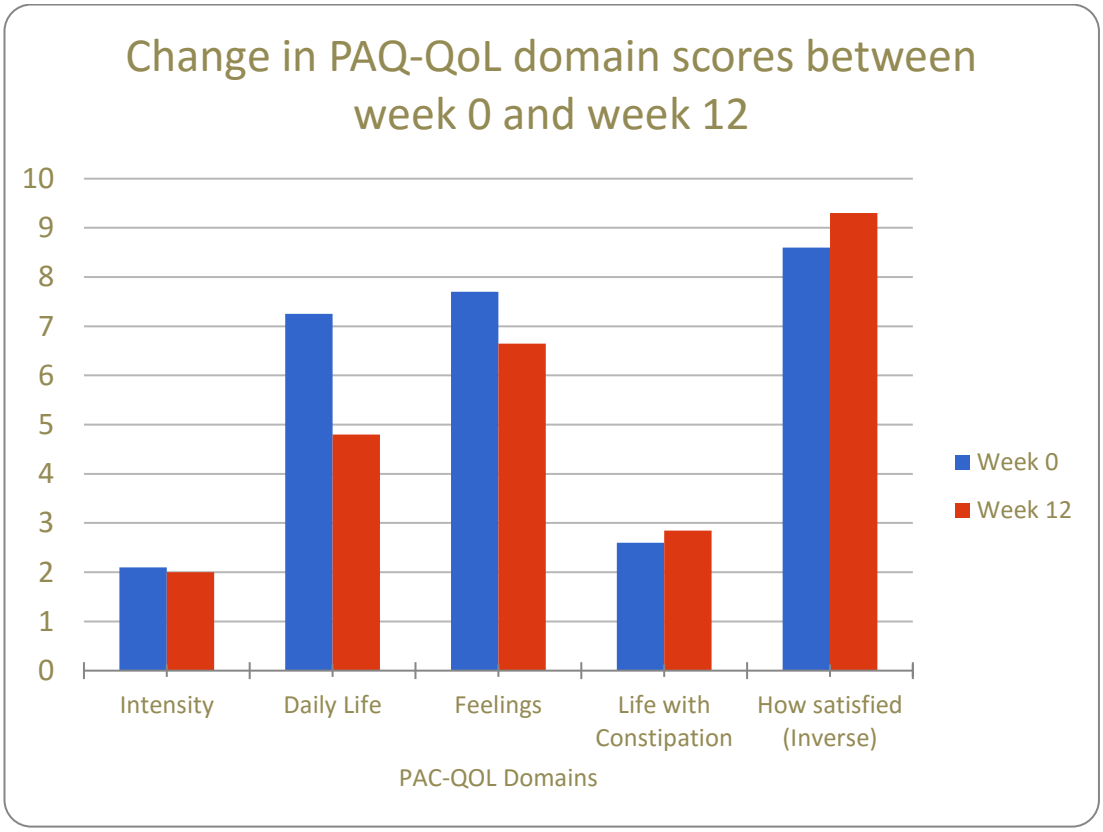


Table 8.8 Table to show the paired t-tests for individual PAC-QOL domains and overall PAC-QOL scores from week 0 to week 12.

PAC-QOL Domains	Mean at week 0 (SE)	Mean at week 12 (SE)	Paired Differences					
			Mean difference	BCa 95% Confidence Interval of the Difference		t	df	Sig. (2-tailed)
				Lower	Upper			
PAC-QOL Domain total score: "Intensity"	2.1 (0.55)	2.0 (0.53)	0.100	-0.678	0.950	0.237	19	.815
PAC-QOL Domain total score: "Daily Life"	7.25 (1.86)	4.8 (1.16)	2.450	-0.258	5.100	1.907	19	.072
PAC-QOL Domain total score: "Feelings"	7.7 (2.0)	6.65 (1.63)	1.050	-2.251	4.500	0.663	19	.515
PAC-QOL Domain total score: "Life with Constipation"	2.6 (0.72)	2.85 (0.77)	-0.250	-1.970	1.370	-0.333	19	.743
Inverse score of PAC-QOL Domain total score: "How Satisfied"	8.6 (1.13)	9.3 (1.3)	-0.700	-3.000	1.400	-0.636	19	.532
PAC-QOL Total	28.25 (5.57)	25.6 (4.5)	2.650	-5.250	10.444	0.716	19	.483

a. Unless otherwise noted, bootstrap results are based on 1000 bootstrap samples

PPBC

Paired T-Test Patient Perception of Bladder Condition (PPBC)

Of the 20 subjects, the average PPBC score decreased between week 0 ($\overline{x}$ = 4.55, SE = .24) and week 12 ($\overline{x}$ = 3.2, SE = .24). This difference of 1.35 points, BCa 95% CIs [1.8, 0.9], was statistically significant $t_{(19)} = 5.81$, $p < 0.001$, and reflects a large effect size, $g = 1.165$. This is displayed graphically in Figure 8.7.

Overall this represents:-

Improvement from baseline – 63%

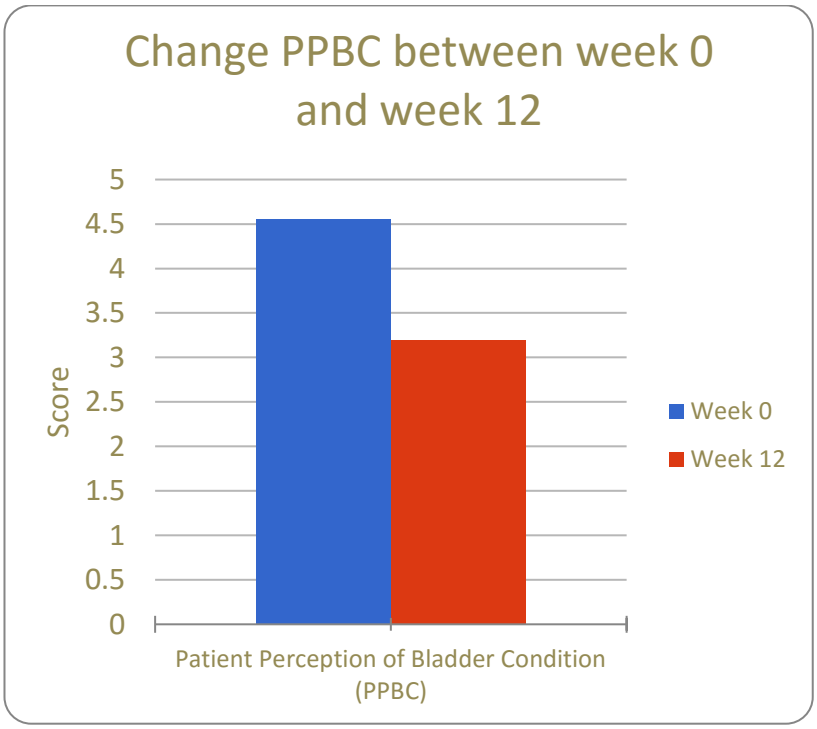
No change form baseline – 29.6%

Deterioration from baseline 7.4%

Mean score at week 0 = 4.55 = my bladder causes me moderate problems

Mean score at week 12 = 3.2 = my bladder causes me minor problems

Figure 8.7



UDS variables

Paired T-Test First Sensation

Of the 16 subjects, the average bladder capacity (in ml) at which participants first experienced the sensation to void increased between week 0 ($\bar{x}$ = 193.4, SE = 31.3) and week 12 ($\bar{x}$ = 232.5, SE = 29.6). However, this difference of 39.1 ml, BCa 95% CIs [31.05, -93.13], was not statistically significant $t_{(15)}$ = -1.41, p = .179, and reflected only a modest effect size, g = 0.28. This is demonstrated in figure 8.8.

Paired T-Test Maximum Cystometric Capacity

The average maximum cystometric capacity (in ml) prior to voluntary void increased between week 0 ($\bar{x}$ = 383.4, SE = 25.6) and week 12 ($\bar{x}$ = 420.6, SE = 28.7). However, this difference of 37.2 ml, BCa 95% CIs [17.72, -85.35], was not statistically significant $t_{(15)}$ = 1.62, p = 0.126, and reflected only a modest effect size, g = 0.3. Demonstrated in figure 8.9.

Paired T-Test Time to First Detrusor Contraction

The average time to first detrusor contraction (in minutes) decreased between week 0 ($\bar{x}$ = 5.1, SE = 1.80) and week 12 ($\bar{x}$ = 4.53, SE = 1.13). However, this difference of -0.17minutes, BCa 95% CIs [2.1, -0.9], was not statistically significant $t_{(15)}$ = 0.572, p = 0.598, and reflected only a modest effect size, g = 0.094. Demonstrated in figure 8.10.

Figure 8.8

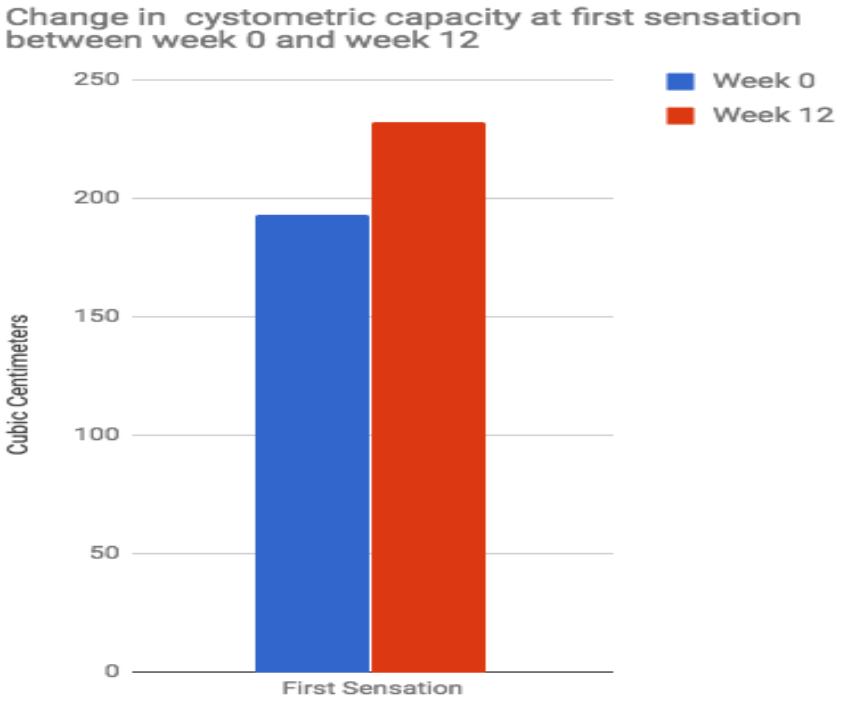
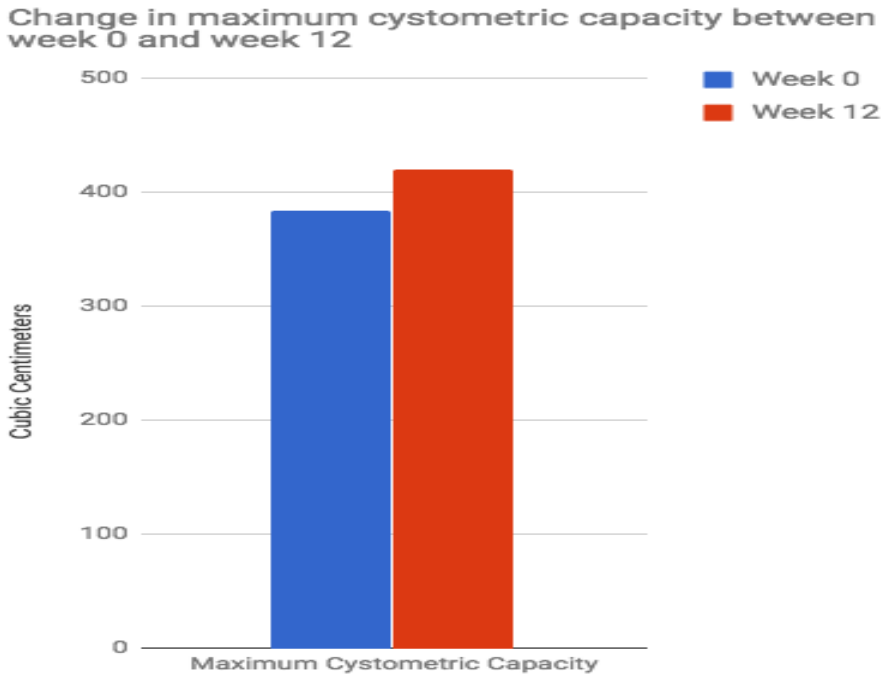


Figure 8.9



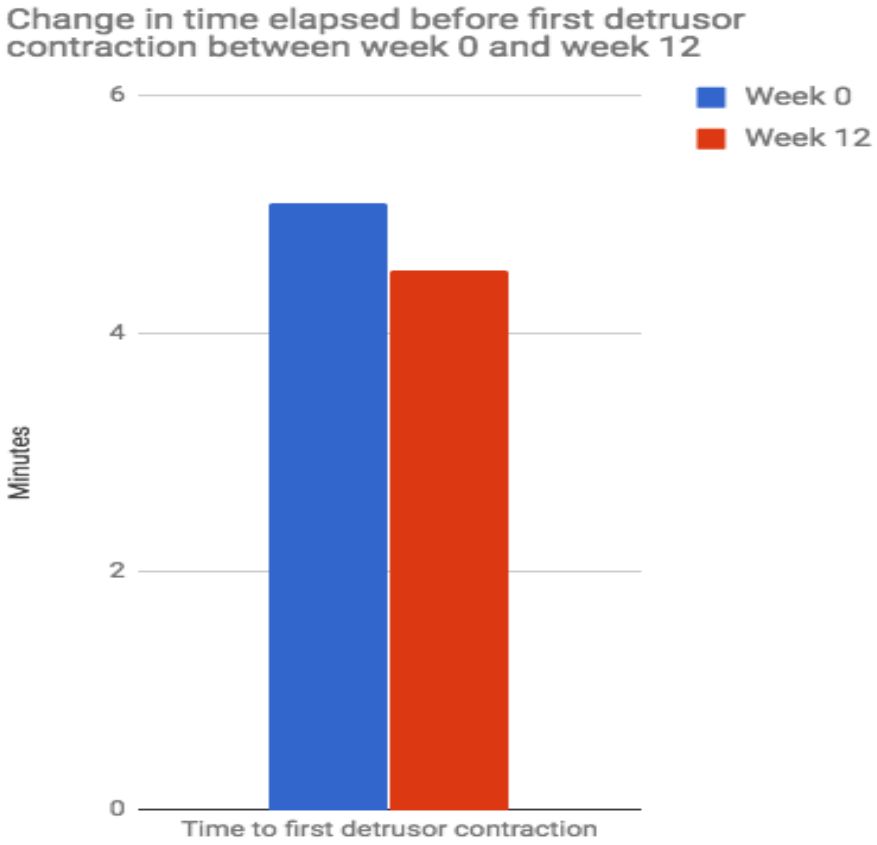

Change in time elapsed before first detrusor contraction between week 0 and week 12
Week 0
Week 12
6
4
2
0
Minutes
Time to first detrusor contraction

Figure 8.10

Urodynamics variables	Mean at week 0 (with SE reported in brackets)	Mean at week 12 (with SE reported in brackets)	Paired Differences						Effect Size (corrected Hedge's g)
			Mean difference	BCa 95% Confidence Interval of the Difference		t	df	Sig. (2-tailed)	
				Lower	Upper				
First Sensation	193.38 (31.27)	232.5 (29.62)	39.13	-93.13	31.05	-1.411	15	0.179	-0.284
Maximum Cystometric Capacity	383.44 (25.6)	420.63 (28.7)	37.19	-85.35	17.72	-1.621	15	0.126	-0.302
Time to first detrusor contraction	5.1 (1.80)	4.53 (1.13)	-0.57	-0.9	2.1	0.572	15	0.598	0.094

Table 8.9 Mean changes in urodynamics variables

In order to determine if SF and QoL outcomes were independent of UDS variables regression models were developed and analysed at week 0 and week 12. UDS variables were not a good predictor of any of the scores on the PISQ-12, SQOL-F or PAC-QOL. The results of the regressions with the KHQ were not significant. All the regression models at week 0 and week 12 have been included in the appendix.

SAGA Questionnaire

All subjects completed the first assessment, SAGA questionnaire. The subject's own treatment goals and assessment of achievement will be discussed in Chapter 9 and have not been included in this analysis.
The three most important goals for the subjects in this trial were to 'reduce the sensation of pressure that prompts me to go to the toilet', 'reduce the sudden need to rush to the toilet' and to 'reduce the number of times I go to the toilet throughout the day'.

Table 8.10 Demonstrates results of the pre-set goals related to symptoms and goal achievement. The mean importance and mean goal achievement for each pre-set goal has been calculated.

Overall the goal 'to reduce the number of times I go to the toilet throughout the day' was the only one that was achieved by most of the subjects and this is reflected in the bladder diary results. All of the goals linked to symptoms associated with OAB were somewhat achieved with the exception of 'reduce the sensation of pressure in my lower abdomen', whereas goals associated with other LUTS were not achieved.

Table 8.10 SAGA Questionnaire results

Pre Set Goals (SAGA Domains)	**Mean Importance of achieving goal** 1= not very important 5=very important	**Mean Goal Achievement** 1= did not achieve 2=somewhat achieved 3=achieved 4=exceeded goal 5=greatly exceed goal
1. Reduce the number times I go to the toilet throughout the day	4.52	3.15
2. Reduce the number of times I get up at night to go to the toilet	3.81	2.65
3. Reduce the sensation of pressure in my lower abdomen	3.59	1.95
4. Reduce the sensation of pressure that prompts me to go to the toilet	4.78	2.45
5. Reduce the difficulties I have completely emptying my bladder	2.93	1.3
6. Reduce the difficulty starting or maintaining a urinary stream	2.63	1.65
7. Reduce the urine loss when I cough, laugh, exercise or sneeze	2.96	1.7
8. Reduce my urine leakage	3.96	2.55
9. Reduce the sudden need to rush to the toilet	4.70	2.75

The correlation between the self-reported importance of a goal and the extent of its actualisation after 12 weeks was evaluated using Kendall's tau statistic. The correlation parameters for each SAGA domain are reported in the table 8.11 below (BCa bootstrap 95% CIs reported in square brackets). The only domain that reached significance was 9. 'Reduce the sudden need to rush to the toilet'.

Table 8.11 The correlation between goal importance and goal achievement for each SAGA domain

SAGA Domain (As described in Table 8.18)	**N**	**Coefficient**	**Significance**
1	20	-0.57 [-0.365, 0.268]	0.775
2	18	-0.71 [-0.410, 0.279]	0.737
3	15	-0.413 [-0.656, -0.095]	0.084
4	19	-0.315 [-0.561,-0.081]	0.145
5	12	-0.22 [-0.648, 0.252]	0.413
6	12	-0.221 [-0.619, 0.241]	0.415
7	13	-0.33 [-0.666, 0.142]	0.184
8	17	-0.191 [-0.694, 0.361]	0.385
9	19	-0.39 [-0.622, -0.113]	0.06

When considering overall goal achievement in the study only one subject did not achieve her goals with a further 35% somewhat achieving their goals. 60% of subjects achieved their goals with 40% of those exceeding or greatly exceeding their expectations. Table 8.12 Demonstrates the breakdown of goal achievement.

Table 8.12 Overall goal achievement according to the SAGA questionnaire

Goal Achievement	Number of subjects (%)
1. Did not achieve goals	1 (5)
2. Somewhat achieved goals	7 (35)
3. Achieved goals	4 (20)
4. Exceeded goals	7 (35)
5. Greatly exceeded goals	1 (5)

Safety & Tolerability

Fesoterodine was well tolerated and no subjects discontinued the medication due to poor tolerability. There were no new safety concerns reported or cases of urinary retention. The serious adverse event of pregnancy in one patient resulted in the patient being withdrawn from the trial. Appropriate scans and assessments were performed along with the necessary documentation and notification to the MHRA. It transpired that the subject had had an episode of unprotected sex the weekend before starting the trial and had taken the morning after pill. When the baseline visit pregnancy test had been performed it was only 2 days after the unprotected sex, hence it was negative. Given the lack of information regarding the impact of fesoterodine in the early stages of pregnancy the subject was counselled accordingly. However, even before this information she had decided that

she did not wish to continue with the pregnancy and was referred to the termination of pregnancy service.

The most common AE reported by subjects was dry mouth by 37% of subjects with 60% reporting this as mild and 40% stating that it was moderate in severity. Two subjects were treated for a urinary tract infection during the course of the study. Bloating, constipation and blurred vision are also commonly associated side effects with fesoterodine but were only reported by one subject each. The subject who reported a chest infection was enrolled in the trial over the winter period and it is presumed that this was associated with the time of year rather than fesoterodine.

All the AE's reported are documented in table 8.13.

Table 8.13 Adverse events reported

Subjects with AE's	**No of subjects affected (%)**
Dry mouth	10 (37)
UTI	2 (7.4)
Bloating	1 (3.7)
Constipation	1 (3.7)
Blurred vision	1 (3.7)
Chest infection	1 (3.7)
Labrynthitis	1 (3.7)
Pregnancy	1 (3.7)

Six months follow up

No new AE's were reported. 60% continued on fesoterodine and were happy with their LUTS. 10% chose to try an alternative anticholinergic to see if that would improve their OAB whilst 10% opted to try the addition of mirabegron to their fesoterodine to see if this would improve efficacy. One subject was referred for further investigation in view of other LUTS and two were escalated onto more invasive treatment in the form of Percutaneous Tibial Nerve Stimulation (PTNS) and Intra-detrusor injections of Botox. One subject chose to try to manage her symptoms conservatively without any medication. These are demonstrated in table 8.14

Table 8.14 Treatment at six months

Treatment at the 6 months point	**No of Patients (%)**
Continued with fesoterodine	12 (60)
Alternative anticholinergic	2 (10)
Combination therapy of fesoterodine and mirabegron	2 (10)
Further investigations	1(5)
PTNS	1(5)
Botox	1(5)
No treatment	1(5)

Conclusions

These results have demonstrated that in this cohort of women fesoterodine appeared to improve sexual function as well as improve their OAB symptoms, QoL and most of the women achieved their goals with therapy. A more detailed discussion linking these findings to the current literature and suggesting new areas for investigation will be presented in Chapter 9.

Although there are trends noted within the data collected, as the recruitment figures were so low it is difficult to comment on what would have been a significant result. It is possible that a statistician could perform a new power calculation based on these results to see if they generate a smaller sample size that may be more feasible in clinical practice.

Chapter 9

Discussions of quantative results and development of the further research questions that emerged from and during this study

Introduction

Following on from the analysis of the trial data presented in Chapter 8, this chapter aims to discuss the quantative findings of the study, reviewing the baseline demographics of the participants and examining the results of both the primary and secondary outcomes. Comparisons to published studies will be highlighted and possible rationales for observations will be suggested.

The chapter will detail the limitations and weaknesses of the study and the potential impact that they may have had on the final results presented and what has been learnt from these. Challenges with the local clinical trials office, ethical, MHRA and national portfolio approvals are addressed and explained. Finally, as the study progressed and during the analysis, there were several challenges that arose and further research questions that developed. These new areas of investigation which were pursued will be introduced prior to further discussion in later chapters. The results of the qualitative findings will be presented in chapter 10.

Despite the fact that this study only recruited 28 subjects, we were able to show statistically significant results in both the primary and many of the secondary endpoints albeit with wide confidence and a moderate effect size (as presented in Chapter 8). Typically, the smaller the study population the more variation in outcomes and the larger the study population the more likely to find statistically significant differences in outcomes. Given the fact that this study showed significant results with the small sample, it is likely that a bigger group may have just narrowed the CIs and increased the effect size. In this case a type 1 error is unlikely as the study showed statistically significant results in both the primary and many of the secondary outcomes.

This means that we have been able to show an improvement in SF following treatment with fesoterodine in women with OAB. However, the fundamental issue with the methodological design of the study means that due to the lack of a comparison group in this study it cannot be determined if this effect is related to fesoterodine or due to a placebo effect. Traditionally in OAB

studies, the placebo effects accounts for approximately a 30% improvement in symptom outcomes. This effect in this study is of that order, however, the placebo effect on SF in OAB trials has not been studied so we cannot say if the results are due to the effect of the drug or the potential therapeutic effect of having a personal conversation with a health care professions about SF and an opportunity to discuss concerns / understands norms etc.

Therefore, this study has either demonstrated the placebo effect of a clinical trial on SF or the potential for fesoterodine to improve SF in women with OAB.

Baseline demographics

The cohort of subjects recruited into this study were similar to other OAB trials reported with the exception that there were a slightly higher number of ethnic minorities, however, this is in keeping with our local population.

All bar one subject had previously tried another medication for her bladder symptoms. This was to be expected as the study recruited women from a secondary care setting and in line with NICE CG171 (2013), first line drug therapy should have been commenced in primary care by the GP. The only treatment naïve subject had declined first line drug therapy by the GP opting for conservative management only until she had a definitive diagnosis.
The length of time that subjects had been experiencing OAB symptoms was wide ranging and if the trial had met recruitment targets it may have been interesting to investigate whether the length of time a subject has been symptomatic influences outcomes. However, there are too few patients to make any further comment on this.

There was a greater OAB wet population than OAB dry in this study (81.5%), however, the frequency of UUI was low with a baseline UUI rate of 1.68 episodes per week. This low frequency of UUI may bias the group as increased frequency of UUI has been reported to result in increased bothersomeness or impact on quality of life (Cetinel et al 2006). If this had

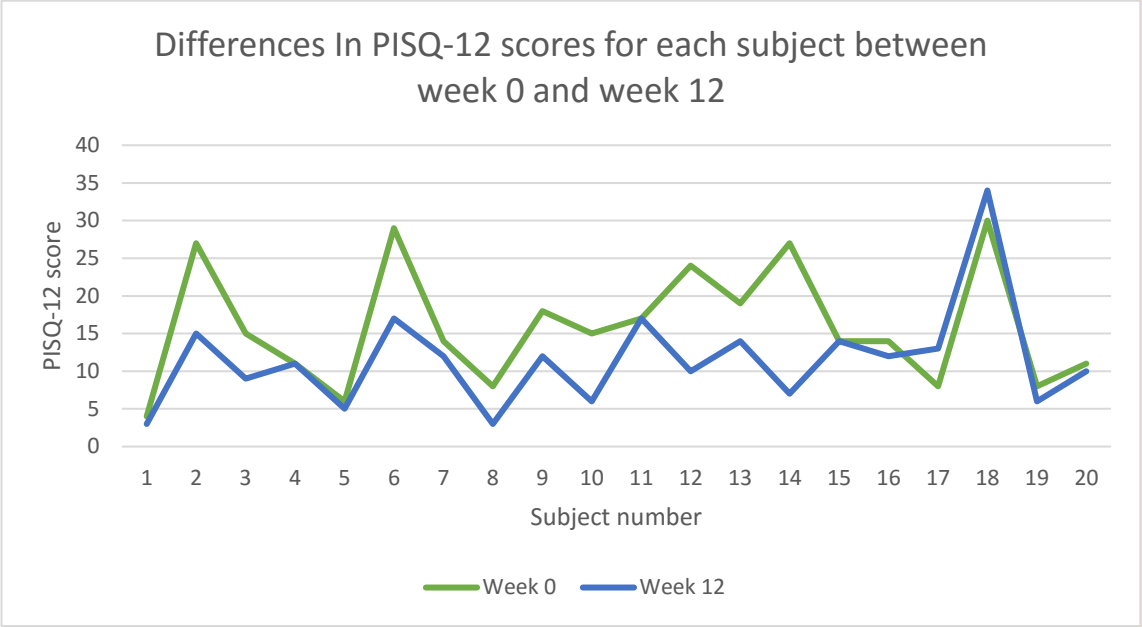
been the case and the analysis met the appropriate power it could be suggested that this study sample was not representative of the OAB population yet with such small numbers no further speculation is warranted.

The percentage of subjects who chose to dose escalate was 53.7%. This is in keeping with the findings from the systematic review on dose escalation in other clinical trials where it ranged from 51-63% (Wyndaele et al 2014).

Primary Outcomes

Overall both of the primary outcome measures demonstrated improvements in SF following twelve weeks of treatment with fesoterodine. The Minimally Important Difference (MID) is defined as the difference in score that is representative of what patients and clinicians perceive as beneficial or harmful and which would justify (in the absence of bothersome side effects or cost) a change in the patients management (Barber et al 2009). According to Mamik et al (2014) the MID for the PISQ total score is 6 points and improvements that meet this threshold can be considered clinically important. In order to compare the long and short form scores the mean change from baseline to week 12 is multiplied by 2.58, therefore, for this study it is 11.223 so well above the MID. This may indicate the potential benefit of fesoterodine in improving the SF of women with OAB, but may also be a placebo effect. The differences in PISQ-12 scores in each subject over the 12 weeks of the study are demonstrated in Figure 9.1.

Figure 9.1 Differences in PISQ-12 scores for each subject between week 0 and 12.



The SQOL-F questionnaire assesses sexual quality of life in three different dimensions: self esteem, emotional issues and relationship issues, however, no MID has been reported in the literature for this questionnaire.

The greatest change in a single item score on the PISQ-12 was seen in Q7 “Does fear of incontinence restrict your sexual activity?” It has previously been reported that UI during SA can increase anxiety and psychological burden on the patient and this can cause pain and discomfort during SA and difficulty achieving orgasm (Coyne et al 2009a). In Italian women, fear of leakage and its consequent embarrassment has been shown to prevent women from participating in sexual activities (Tubaro 2004) Nicolson et al (2008) performed focus groups and interviews with people with OAB to understand the psychological consequences of their symptoms and the impact on their QoL. Participants described anxieties related to body image / self-esteem and the fear of leakage that was triggered by anxiety and previous experiences and led to restrictions in sexual activities

In this study, many of the women reported a reduction in incontinence during SA following 12 weeks of fesoterodine (see table 8.3) and it could be hypothesised that in line with this reduction of leakage experienced, the anxiety / fear of UI reduced and resulted in less restrictions in SA. A larger cohort would be needed to fully assess this idea.

In the literature review, it had been noted that typically anticholinergic medication can have a negative impact on the arousal domains of SF but in this cohort there was no difference noted between week 0 and week 12 in the arousal domains of the PISQ-12 (Questions 1 and 3).

The greatest improvements from baseline (eg reduction in score) on the SQOL-F were seen in Q7 'When I think about my sex life I feel anxious' and Q10 'I worry about the future of my sex life'. This mirrors the findings in the EPILUTS study where participants with OAB reported significantly more worry over the future of their sexual life (Coyne et al 2011).

It has been demonstrated that symptoms associated with OAB can be detrimental to psychological wellbeing as well as on a physical level (Toozs-Hobson 2010). A systematic review by Kinsey et al (2016) reported on seven studies that compared anxiety levels in OAB patients to non OAB controls. All the studies described significantly higher levels of anxiety in the OAB groups compared to the controls, with OAB wet patients reporting higher levels of anxiety compared to those with OAB dry. Additional studies corroborate these results in older populations and in other types of urinary incontinence (Mehta et al 2003, Lim et al 2007, Knight et al 2012, Alves et al 2014).

For many years it has been suggested that psychosomatic disorders e.g. anxiety may play a role in the pathogenesis of OAB (Freeman et al 1985). According to a prospective longitudinal study by Perry et al (2006), 56.6% of women with UUI report symptoms of anxiety and 37.6% described symptoms of depression. However, incident cases of UUI can be predicted by anxiety at baseline and it was noted in the study that anxiety, UUI and frequency

appear to interact and exacerbate each other. Sakakibara et al (2013) reported that anxiety and depression are a cause of bladder dysfunction, particularly OAB, and that the bladder is under emotional control. This would then pose the question of which came first – the OAB or the anxiety / depression? In the study for this thesis, this question was not considered when recruiting women but it is unlikely that it would have had any impact on the outcomes due to the small numbers in the trial. In future however, one may consider adding this question to the baseline assessment.

It would have been interesting to compare the psychological domains of the QoL and SF questions in the OAB wet and dry groups to see if there are any differences in the outcomes of treatment. However, due to the small numbers of women recruited into the study, the groups would have been too small for meaningful analysis.

There were also considerable improvements seen in the single item scores on the PISQ-12 related to pain during intercourse / negative emotional reactions / intensity of orgasms and fear of UI. It could be hypothesised that if women no longer fear UI during intercourse, it may reduce their anxiety, improve body image and allow them to relax during sex, reducing pain and potentially improving orgasms.

When looking at the difference in individual questions on the PISQ-12, no difference was reported in Q3. 'Do you feel sexually excited when having SA with your partner?' And Q10 'Does your partner have a problem with erections that affects your SA?' This could be expected as all subjects recruited were in stable sexual relationships so there were no new sexual partners introduced and no intervention was provided for the partners. However, for the women who's SF improved during the study, as they started to feel better about sex it could have increased sexual excitement but this was not observed , If partners had pre-existing problems with erections, it was presumed that this would be the same throughout the course of the study. Although there is evidence to suggest that the partners of women with UI have reduced SF (Beji et al 2005, Bekker et al 2010), no assessments of

partners were included in this study and there is no evidence that partners experienced improvements in SF or erection quality if the woman's UI was treated.

The smallest changes on the SQOL-F was also seen in the partner related aspects of the questionnaire with most women reporting that they feel close to their partner and that they are able to talk to them about sexual matters. Only a few women in this cohort worried that their partner felt hurt or rejected by their sexual concerns.

Secondary outcomes

When reviewing the efficacy outcomes it is important to consider what a clinically important difference is to the patient. The minimal clinically important change in the number of UUI episodes has been shown to be a reduction of more than three UUI episodes per week from baseline (Homma & Koyama 2006). In this study 81.5% of subjects were wet at baseline. According to the bladder diaries, the mean change in number of UUI episodes per day was -1.02 and this would result in a reduction of over double the threshold of 3 episodes per week, indicating a clinically important change. Within the primary outcomes, the impact of anxiety associated with UUI was highlighted as a significant factor for women. Yet in the study quoted above it was not recorded how many episodes of UUI make somebody anxious. Due to the subjective nature of this, a future study investigating anxiety levels and UUI episodes would be interesting, although one would hypothesise that this is multifactorial based on personality and resilience as well as the physical symptoms.

Another measure that can also be considered is dry rates (ie those who reported UUI at the start of therapy but this has now resolved). In this study 64.7% of subjects reported no longer experiencing UUI after 12 weeks on fesoterodine. This is in keeping with other studies where the dry rate was 64% (Herschorn et al 2010a). Women also reported a 68.3% reduction in

urgency at the 12 week point and again this is in keeping with the FACT study which showed a 71.4% reduction in urgency (Herschorn et al 2010a).

Nocturia was not found to be a particular problem within the current study with the median number of nocturia episodes per 24 hours was only 1 at baseline and 0 at week 12. When considering the prevalence of nocturia in women it has been reported to affect between 5.4-7.9% of pre-menopausal women and 13.3-17.6% of post-menopausal women (Rekers et al 1992, Samuelsson et al 1997). A systematic review of nocturia reported that women over 60 years old are four times more likely to report nocturia than women under 60 years (Pesonen et al 2016). Given that only three women (35.7%) in this group were over 60 and 14 (64.3%) were pre-menopausal these low rates of nocturia are not unexpected.

Overall, a 30% reduction in the number of voids per day from baseline was reported. This is slightly higher than in some of the other studies which have reported reductions in frequency of 18.9-23.5% (Kaplan et al 2011, Herschorn et al 2010a). There was however a significant reduction in fluid intake (18%) over the course of the 12 weeks of the study that may account for this. This effect could just be a result of the small numbers in this cohort and unrepresentative of the OAB population or as a result of inadvertent advice given to patients in the study as they were attending our Urogynaecology unit where information leaflets are freely available and posters are on display recommending lifestyle changes that may help improve bladder symptoms.

The minimal improvement in HRQL that confers clinical benefit to the patient is a change in KHQ domain scores of ≥ 5 points from baseline (Kelleher et al 2004). This was seen in every domain of the questionnaire in this analysis. The highest domain scores at baseline, indicative of greatest impairment, was reported for incontinence impact, followed by role limitations and physical limitations. The greatest improvements at week 12 were seen in role limitations, followed by emotions and incontinence impact. This improvement in emotions may also link in with the reduction in anxiety /

depression and improvement in self-esteem noted in the primary outcomes. In the pooled analysis of fesoterodine on QoL, the greatest improvements were seen in incontinence impact, role limitations and physical limitations so the findings of this study are in keeping with previous work (Kelleher 2008). These improvements in HRQL are not just similar to other studies using fesoterodine but are also in line with other treatment modalities eg onabotulinum toxin A (Botox) (Nitti et al 2013, Ginsberg et al 2017). The least change was seen in the general health perceptions domain but this is to be expected as it is a marker to show that the questionnaire works in this population.

The PAC-QoL questionnaire provided us with very little information in this study. This may be because none of the subjects had specific problems with constipation at the start of the study and only one reported constipation as an adverse event. When the study was designed, this outcome was added as constipation is often quoted as the second most common adverse effect of anticholinergic medications after dry mouth, yet there is little understanding regarding how bothersome this is, hence the choice of questionnaire. It is difficult to predict based on these results if this outcome would be different had full recruitment targets been met. However, if designing this study again, potentially the International Consultation on Incontinence- bowel symptoms questionnaire (ICIQ-BS) would be adopted, as by using this modular questionnaire, results can be pooled and compared with other studies. Constipation is reported as an adverse event in many studies using anticholinergics and often quoted as a reason why people stop therapy. The lack of impact on constipation and QoL in this study is surprising and deserves further investigation.

When reviewing the outcome of the PPBC, 20% of the subjects did not report any difference after 12 weeks of treatment with fesoterodine and this is in keeping with the findings of the FACT studies.

The UDS outcomes were added to the study when supervision for this degree was changed from the School of Nursing to the Faculty of Life

Science and Medicine. It was considered an exploratory idea to investigate whether SF and QoL outcomes were independent of UDS variables. Originally, the plan was to recruit 40 subjects into this arm but only 16 were included in the final analysis.

When comparing pre and post treatment UDS, there were no significant increases in first sensation to void, maximum cystometric capacity or time to first detrusor contraction. For those who had DO at baseline, 50% did not have repeat UDS (either because they were no longer in the study or did not consent), 31% still had DO at 12 weeks and 19% DO did not occur on UDS.

Regression models were developed to determine if the outcomes of the PISQ-12, SQOL-F, KHQ and PAC-QoL at week 0 and 12 were independent of UDS variables. However, no trends could be identified. Again this could be because recruitment to this part was still under 50% of the original target, however, as this was an exploratory idea it could also mean that SF and QoL outcomes are independent of UDS variables but this cohort is not large enough to confirm this. Previous work has demonstrated that treatment efficacy with fesoterodine is independent of the UDS diagnosis (Nitti et al 2010a).

The most important goals set by subjects were ‘to reduce the sensation that prompts me to go to the toilet’, ‘reduce the sudden need to rush to the toilet’ and ‘to reduce the number of times I go to the toilet throughout the day’. These are the same as those reported in the SAFINA Study and relate to the cardinal symptom of OAB, which is urgency and associated urinary frequency (Cardozo et al 2012). The least important goals were related to maintaining urinary stream, emptying the bladder and reducing stress incontinence and none of these goals were achieved. This is to be expected as this cohort have all been assessed to ensure that they were emptying their bladders and all had urgency predominant symptoms. The only goal completely achieved was related to reducing urinary frequency. This is not surprising considering the 30% reduction in urinary frequency noted on the bladder diaries that has previously been discussed. The goals related to

reduction in urgency and UUI were somewhat achieved and this is in line with the 64.7% dry rate and 68.3% reduction in urgency demonstrated.

Overall goal achievement was 60% compared to the 50% in the SAFINA study but this may be due to the difference between having men and women in the study and issues around maintaining urinary stream which was flagged as an important goal in the SAFINA study but not in this group and mainly relate to men rather than women.

In line with many other studies previously discussed, fesoterodine proved to be a safe and well tolerated drug. As with all studies on antimuscarinincs, the most common adverse effect was dry mouth. The rate of dry mouth in this cohort was 37% and this is in line with findings from other studies where it ranged from 33.8-37.7% (Herschorn et al 2010b, Kelleher et al 2012). However, it was not severe enough to result in any discontinuations from the study.

Literature has reported 6 months persistence rates for anticholinergics in the real world ranged from 28% to 46% (Yeaw et al 2009, Wagg et al 2012). In a pooled analysis of the Chapple (2007) and Nitti (2007) long term extension trials, 49% of subjects continued on fesoterodine for two years (Kelleher et al 2012). In this study, 60% of subjects continued with therapy at the six month stage. This is quite high and could still be due to the effect of being monitored in a clinical trial and would be likely to reduce over time were they to be assessed at the one or two year point. The most common reason for stopping treatment was lack of efficacy in line with most other trials of anticholinergics (Benner et al 2010).

Methodology Discussions

Issues with study set up

Once confirmation that funding had been awarded was received in 2010, the first stage of the approvals process was to get the Joint Clinical Trials Office (JCTO) involved as they would be sponsoring the project. They provided specific guidelines and structures that were necessary for CTIMP's and would be checking the protocol and submissions to the REC, R & D and MHRA. Unfortunately, the clinical research associate (CRA) assigned at the beginning of this study did not make decisions well and did not manage processes in a timely manner. A table has been included in the appendix to demonstrate the time delays and barriers faced at each step of the way when trying to get this protocol and IRAS form fit for submission and approval.

During the course of this study the JCTO underwent a major restructuring and management changes and is now called the King's Health Partners Clinical Trials Office (KHPCTO). There have been many staff changes and this study has had six different CRA's throughout its course which has caused endless delays / confusion and duplication of work within the monitoring process. In the light of other research issues within the hospital, a meeting was convened between the hospital R&D team, all the local PI's and the JCTO. This study was used as an example of barriers in the research process and a full apology has been issued by the KHPCTO.

Issues with recruitment

The most fundamental issue with this study has been with the lack of recruitment. Once approvals were in place and IMP was available, it was hoped that 10 women per month could be recruited from clinics.

However, the site had real difficulty finding women who met the inclusion and exclusion criteria who were willing to take part. After the first couple of months of only recruiting one subject per month, action was taken so that

research posters were put up in all the toilets in the women's outpatients department, and flyers were in all waiting rooms. Research flyers were also sent out to all patients in their UDS appointment packs and to all those attending the bladder retraining classes. Women were approached in their clinic appointments to enquire about joining the study but still the site was struggling.

After 9 months, discussions took place with the investigators clinical supervisors to try to enhance recruitment. It was suggested that the second supervisor's hospital – Guy's and St Thomas' Hospital (GSTT) could be used as a patient identification centre (PIC) and potential subjects could be directed to the study team for screening. A substantial amendment was successfully submitted to the REC and research posters and flyers were again put up in the toilets in the women's outpatient department and provided in waiting areas at a second hospital. Although this resulted in a substantial number of women phoning the research site or contacting the investigator by email, unfortunately none of them were suitable to recruit due to a variety of issues but most commonly that women had not correctly read the poster and were not sexually active (NSA).

After a further 3 months, recruitment had still not improved so the decision was made to include additional research sites. Through discussion with the PI, three additional sites were identified in large Urogynaecology units across London.

The units were all well versed in carrying out CTIMP's in women with OAB and given that the study was on the National Portfolio it made it profitable to their departments to be involved. In September 2013, Imperial College Hospital Trust were confirmed as a recruitment site and then in May 2014 (due to delays in the JCTO with contracts) Croydon University Hospital and Medway Hospital were also initiated as research sites.

The investigator performed the set up visit at all of these sites, created all of their site specific documentation and site files and to encourage competitive

recruitment offered a night out for dinner in London for the research team that recruited the most subjects. Sites were emailed every other month for updates on recruitment.

One year later in July 2015, recruitment was still very low at the index site and none of the additional sites had managed to recruit a single subject. A meeting was held with the investigators clinical supervisors and questions raised to identify why we could not recruit women into this study. From the investigators own experience, reasons for poor recruitment included a lack of women who were actually SA, and for those who were SA many did not meet the inclusion criteria frequency of once a week. Several women had failed screening due to their bladder diaries not meeting inclusion criteria of 8 voids per 24 hours. Feedback was sought from the other sites who also reported women screen failing on the once a week sexual frequency as well as women not wanting to discuss the issue or complete personal questionnaires. One site reported that the reason women had declined was because they did not want to complete so many bladder diaries.

Based on these discussions the investigator and PI went back to the research protocol and reassessed each of the inclusion / exclusion criteria. The two main concerns identified were inclusion criteria 3 and 5. Inclusion criterion 3 was one of the criteria taken from the SAFINA study as was a common requirement in all OAB trials. However, in 2010 the definition of frequency according to the joint terminology report from ICS / IUGA changed from ‘voiding 8 or more times per day’ to ‘voiding a number of times deemed bothersome by the individual’ but this was not reflected in our protocol and preventing women from entering the study (Haylen et al 2010).

Issues with SA

When inclusion criterion 5 was set, it was to provide an arbitrary frequency of SA so that subjects were SA regularly during the course of the 12 weeks of treatment and hence may notice a difference. It was felt that if women were only SA one or twice during this time changes may not be noticed. However,

many women were reporting that they were NSA that often and this meant a lot of women failed the screening. One of the difficulties of setting this figure had been in relation to variations in SA according to age especially as the age range for this study was 18-80 years. In 2013, data were published quoting the average frequency of SA per month according to age range and it varies from 5.8 to 1.4 times per month (Mercer et al 2013). When considering the frequency set in the study on average only women aged under 44 years of age would meet the entry criteria.

Based on these findings a substantial amendment was submitted to the REC requesting a change to the protocol so that the value of more than 8 voids per 24 hours on the bladder diary was removed and replaced with the inclusion of frequency as deemed bothersome by the patient and the frequency of SA of once per week was also removed and replaced with the more open inclusion of SA within the course of the trial but without any set arbitrary figures.

Finally, to allow maximum time for recruitment, study timelines where changed to extend the recruitment period.

Amendments to the study

In view of all the changes to the study related to the recruitment issues discussed above and other logistical issues related to the supply of IMP and extension of timelines there have been many minor and substantial amendments submitted to the REC and R&D and multiple versions of the research protocol as it has been updated. For reference these have been included in tables in the appendix.

Limitations / weaknesses of the study

There are several limitations that have been identified in this study. The most important problem identified was in the lack of a comparator arm for the study. Although the study was consistent with a significant positive effect of fesoterodine on the SF in women, it is not possible to be confident that this is a true result and not just a placebo effect from a health care professional taking an interest in this aspect of their life or from the thought and deliberation on the topic required to complete the questionnaires. The fact that the initial criteria of the study required women to be SA at least once per week, may have invigorated and renewed an interest in their sexual lives not only for them but also their partner and this potential increase in attention may also have had an impact on the results. Looking back at the results there was no significant difference in the desire question on the PISQ-12 or the SQOL_F, however, there was a significant positive change in the score on the SQOL-F related to happiness with frequency of sexual activity which may be related to this.

Since the original power calculation was performed there have still been very few studies performed in women with OAB where SF outcomes are the primary endpoint. However, if the study were to be redesigned now then potentially an alternative SF questionnaire would be employed in the study (the Female Sexual Function Index FSFI) and there are many studies using this questionnaire in a variety of populations. Potentially, with this increase in available data, an alternative power calculation based on a different questionnaire could lead to a reduced number of women required to reach statistical significance which would result in a far more feasible study in this population.

It would be interesting to perform a longitudinal observational study in a cohort of women who are SA, where the only intervention received is time with a HCP when they have the opportunity to discuss their SF and complete questionnaires relating to SF and to repeat the assessment over several time

points to understand not only variations over time but also the impact of this potential package of care. This potential for improvement in symptoms could be considered the same as the learning aspects associated with the use of bladder diaries and improvements seen in diary variables.

The lack of a placebo arm could also be considered as a limitation in this study as it means that findings were not comparable to no treatment (other than a package of care). There have previously been many studies confirming the efficacy of fesoterodine in comparison to placebo (Chapple et al 2007, Nitti et al 2007, Herschorn et al 2010, Kaplan et al 2011). As all subjects in this trial received open label treatment there should be no intervention bias. It also empowered the subjects to choose therapy with the option to dose escalate and the intention of this was to ensure optimum treatment efficacy in the hope that it would in turn result in optimum impact on the primary outcomes. However, it is known that the placebo effect in LUTS has a strong behavioural component as patients become aware of their voiding habits and potential risk factors (Van Leeuwen et al 2006), and this may have had a confounding effect on the efficacy outcomes.

In retrospect we recognise that the trial inclusion / exclusion criteria were too stringent. The main criteria were originally from a trial looking at efficacy and tolerability of flexible dose fesoterodine. The exclusion criteria included an extensive list to try to recruit a 'pure' group with few confounding variables so women who had previously had pelvic surgery, or who took certain medications or were receiving other conservative therapies were all excluded. This allowed the trial to focus on patients most likely to respond to treatment who were unlikely to have an alternative aeitiology behind their SDF. In this study, many women did not even make it to the screening stage, for example those with de novo OAB post successful incontinence surgery. In clinical practice these women would still be offered the same therapy and they may be experiencing the same problems with SF. Thus it is possible that if the exclusion criteria were relaxed to open up the study population, recruitment would be improved. It is appreciated that this would increase the heterogeneity of the group but the study of SF in women with

OAB symptoms and the impact of an intervention such as drug therapy is not an exact science and this may have provided us with a more 'real world' view.

Discussions in relation to the lack of probability sampling methods used in the recruitment of subjects for this study and the rationale for this have been previously provided in the methods chapter. As all patients were recruited from one single site and all data collection performed by one single investigator, this could introduce a selection bias into the findings. Although a single investigator collected all the data and performed all the trial visits, the use of validated and reliable self-reported questionnaires, filled out at appropriate time intervals should prevent any measurement and recall bias.

In total, recruitment to this study took place over four years. It is possible that there may have been confounding factors affecting the results of the trial dependent on the time of year the subjects were recruited. It has been demonstrated that cold weather can negatively impact upon OAB symptoms (Victor et al 2012) and this may result in poorer outcomes. However, in reality the numbers in this study are too small for this to have a significant impact.

Another limitation of this study could be considered with the sample population itself. As this study was recruiting women with OAB and not just DO, some of the subjects may have had the OAB symptoms due to underlying causes which would never respond to an antimuscarinic despite them being widely available and employed for women with OAB not just DO. It is however, hoped that the screening measures employed and exclusion criteria set may have prevented this being an issue. Also, work by Malone Lee & Al-Buheissi (2009) reported that treatment response to antimuscarinics is no different dependent on whether the subject has DO or not so this should not have introduced a bias into the results.

Reflections on Methodology

This study has confronted many problems along the way, not only from a sponsorship / regulatory point but the main issue has been related to the lack of recruitment to the study. Despite multiple attempts to change the protocol and increase the study population available by the addition of research sites only a fifth of the intended numbers of subjects were recruited.

When the protocol was first developed, it was naively believed that due to the extensive experience in the department of conducting CTIMP's assessing treatment efficacy for women with OAB that by adopting a similar approach for this study a pilot study to test the research methodology would not be required. In reality, this study, instead of meeting recruitment targets and allowing the analysis to provide us with statistically significant results based on an appropriate power, has become its own pilot study helping to identify ways in which research methodology needs to differ when assessing sexual function outcomes.

It has highlighted how our knowledge of this patient population, particularly in relation to the prevalence of women with OAB that are sexually active, is deficient and has helped to identify the need for further investigation in women who are not currently sexually active and the reasons why this may be. It could be hypothesised that women may not be sexually active due to their bladder symptoms and that treatment of those symptoms may enable them to re-engage with sexual relationships. Due to the design of this trial, these women would have been excluded therefore future studies in this area should be considered.

Throughout this study there have been many discussions regarding the methodology and what could be the barriers to recruitment. Potential concerns with the inclusion criteria were identified and addressed and no concerns were raised in relation to the tools used to measure outcomes, the sampling methods or trial processes. However, considerations were not made to the non-standardised aspects of this trial, most importantly how the

clinicians approached the women regarding SA and how they took a sexual history. With multiple research sites and trial personnel, there may have been a significant variation in the way in which women were approached, and the depth of discussion on sexual function. One possible change for future studies would be to develop a recommendation of how to take a sexual history and to ensure all study staff are educated appropriately to use standardised introductions to the subject for women and clinicians. This may reduce variations in the discussions regarding SF and foster more open discussions with women and potentially enhance recruitment.

Conclusions

Although this study did not proceed as planned, the results of the secondary outcomes are in keeping with most other clinical trials using fesoterodine. Given these similarities, it is considered that as there were statistically significant improvements in the primary and secondary outcome measures, this does confirm that this is an appropriate area for investigation. There is potential for a positive benefit of fesoterodine for the treatment of OAB on women's SF. However, the design of this study means that we cannot confirm that this was not due to a placebo effect rather than drug effect. Further investigation into the sample population is necessary to determine the scope of the problem and understand how to identify these women in practice so that appropriate and reliable sampling methods can be developed for future studies.

Chapter 10

Qualitative Results

Introduction

This study used a mixed methods approach. A quantitative approach to measuring changes in sexual function associated with the use of Fesoterodine was used and the results are reported in the previous chapter. In addition to this, the Self Assessment Goal Achievement (SAGA) questionnaire was used to allow patients to report their own treatment goals and desired outcomes from therapy.

As previously described in Chapter 6, the SAGA questionnaire contains 9 fixed goals and a further 5 open ended goals where patients were able to set any individual goals or outcomes that they wanted to achieve. The qualitative component of this study involved analysing the data from the open ended patient centred goals to focus more on what is actually important to patients and the true impact of their symptoms on everyday life rather than just using fixed outcomes.

By using qualitative as well as quantitative methods we were able to gain deeper insights and a broader perspective into the ways in which symptoms impact on an individual's quality of life in a manner that captures their own thoughts, views and subjective opinions alongside the objective data gained from the main study.

This chapter describes not only describes the use and analysis of the SAGA questionnaire in this study but I was also offered the opportunity to analyse the qualitative results of the SAGA questionnaire from the UK multicentre SAFINA study. It will therefore include the analysis of the goals from the SAFINA study and comparisons with the cohort of patients from this thesis will be discussed.

Patient centred outcomes

In clinical practice and in research, patient centred outcomes are often utilised to help improve communication between patients and clinicians and

to help manage expectations from treatment. However, many of these goals are generic and do not adequately capture the details of day to day life that bother patients the most and that they hope will improve with therapy.

Patient centred outcomes in Urogynaecology were first described by Brubaker and Schull (2005) who coined the term EGGS to facilitate communication about patient-centred treatment outcomes —E expectations, G goal setting, G goal achievement, S satisfaction. It has been reported that positive physician - patient communication, and setting individualised treatment goals can lead to improved patient satisfaction (Marchall-Kehrel & Spinks 2011). Also, by allowing patients to set their own goals for treatment, and then to self-assess achievement of those goals it may help to capture the effect of OAB and the impact of treatment in a more individualised, patient centred way than disease specific QoL questionnaires in common usage (Cartwright et al 2010). According to Hullfish et al (2002), assessment of patient goals is quick and easy and may help clinicians better understand and care for their patients.

Although goal attainment scoring has been used for different conditions until the development of the SAGA questionnaire by Brubaker et al (2011), there were no self-completed instruments that would allow patients with LUTS to proactively capture their treatment goals for discussion with their healthcare provider in a routine clinical or research setting. The SAGA questionnaire was designed to improve physician-patient interaction and to allow goal achievement to be assessed in research studies. It has been validated and its clinical utility assessed and it has been used in many different research trials for patients with OAB as discussed in Chapter 6 (Brubaker et al 2011, Brubaker et al 2013, and Khullar et al 2013).

The SAGA questionnaire was incorporated as an outcome measure in the study described in this thesis (which will be called Feso and SF for the subheadings in this chapter) and also in the UK Study Assessing Flexible-dose fesoterodine in Adults (SAFINA) (Cardozo et al 2012). The SAFINA study was a 12 week, multi-centre open label study which recruited 331

adults with OAB at 39 sites in the UK from February 2009 to January 2010. During the initial stages of this thesis, the student was offered the opportunity to perform the qualitative data analysis on all the patient goals set in the SAFINA study. This was completed and published as an article entitled 'Personal goals and expectations of OAB patients in the UK' in Neurourology and Urodynamics as well as being presented at National and International meetings.

SAFINA Study – Methodology

The aim of the study was to evaluate the efficacy and safety of flexible dose fesoterodine and the factors associated with dose escalation in subjects with OAB. All subjects were treated with fesoterodine 4mg once daily for the first four weeks and were then given the option to dose escalate up to 8mg for the next eight weeks. Treatment was stopped at twelve weeks and subjects were reassessed at 16 weeks (Khullar et al 2013). At each visit in the study patients completed a 3 day bladder diary and multiple questionnaires to identify patient reported outcomes. A preliminary version of the SAGA questionnaire was included in the study as an exploratory endpoint. Inclusion / exclusion criteria can be found in the main study publication. This study was approved by the appropriate Independent Ethics Committee and conducted in compliance with the ethical principles of the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice Guidelines. Written informed consent was obtained from each subject before entering the study.

Fesoterodine and Sexual Function Methodology

These were the same as described in Chapters 6 and 7.

SAGA Analysis Methodology (as applied to both studies)

The SAGA questionnaire is a patient completed, physician reviewed tool to assess the patient's goals for treatment and whether the goals have been

achieved for subjects suffering from OAB and/or other LUTS. The SAGA questionnaire is in two parts. The first part contains nine fixed goals with a further five open-ended goals. These goals are reviewed with the clinician in order to assess whether they were realistic. The SAGA follow up questionnaire asks the patient to relate the degree of achievement of the original treatment goals set prior to the start of treatment. Multiple clinicians completed the SAGA questionnaire with subjects in the SAFINA study, compared to the single clinician in the Fesoterodine and SF study.

Qualitative Analysis Methodology

This chapter specifically examines the open ended goals that patients chose in relation to what they would most like to achieve from therapy, therefore, in order to determine the most appropriate method of data analysis to be used in this enquiry a review of the literature was performed.

Thematic analysis is a method for identifying, analysing and reporting patterns (themes) within data and is considered as a foundational method for qualitative analysis (Braun & Clarke 2006). It is one of the most commonly used methods for data analysis in qualitative research, however, according to Boyatzis (1998) thematic analysis is not a specific qualitative data analysis method but a tool to use across methods. It is reported that thematic analysis is well suited to large data sets as it allows for categories to emerge from the data and that the interpretation of these themes are supported by the data, however reliability can be of concern if there are different interpretations of the data from multiple researchers (Guest 2012, Saldana 2009). Considering that there would be a large data set and only two researchers it was thought that thematic analysis was the most suitable tool for data analysis and that an inductive approach should be adopted but further decisions on an appropriate methodology was required.

The three most common qualitative approaches used in health research are Phenomenology, Discourse Analysis and Grounded Theory (GT). Discourse analysis aims to understand how people use language to create and enact

identities and activities and was not thought to be relevant to this study. The goal of phenomenology is to describe the meaning of a lived experience of a phenomenon. It uses the description and analysis of a lived experience to understand how meaning is created through embodied perception (Starks & Brown Trinidad 2007). Phenomonologies are often written as stories that allow the reader to get a feel for what it is like to have the experience. GT is used to develop explanatory theory of basic social processes. The idea is that theory is grounded in data and that theory evolves and emerges from the analysis of those data. Thematic analysis takes the concept of supporting assertions with data from GT (Charmaz 2006).

For this analysis it could be considered that both of these approaches have attributes that may seem appropriate, and table 10.1 demonstrates the similarities and differences in the methods.

Table 10.1 Similarities and Differences of the two methods (adapted from Starks & Brown Trinidad 2007)

	Phenomenology	**Grounded Theory**
Philosophy	There exists an essential perceived reality with common features	Theory is discovered by examining concepts grounded in the data
Goal	To describe the meaning of the lived experience of a phenomenon	Develop an explanatory theory of basic social processes
Sampling	Those who have experienced the phenomenon of interest	Those who have experienced the phenomenon under different conditions
Typical sample size	1-10 persons	10-60 persons
Analytic methods	Identify descriptions of the phenomenon; cluster into discrete categories; taken together these describe the 'essence' or core commonality and structure of the experience	Open, axial and selective coding; examining concepts across their properties and dimensions; develop an explanatory framework that integrates the concepts into a core category
Audience	Clinicians, practitioners and other who need to understand the lived experience of the phenomenon of interest	Research and practitioners who seek explanatory models upon which to design interventions
Product	A thematic description of the pre-given essences and structures of lived experience	Generate theory from the range of participants experience

Although the goal of phenomenology seems to fit the research question, the sampling, sample size and analytical methods of GT appear more suitable for the data set given the size, the fact that subjects are coming from many different populations and the depth of coding. The concern with GT methodology is whether theory can be generated from the data. However, according to Stark and Brown Trinidad (2007) although the goal of GT is to

produce theory, it is not uncommon for researchers to identify patterns only within and between categories producing conceptual thematic descriptions rather than explanatory theories. Therefore the decision was made to perform a thematic analysis based on a GT approach.

Grounded Theory Methodology

This methodology was founded by Glaser and Strauss in 1967 in response to a lack of contextualised theories in sociological research (Glaser & Strauss 1967). There have been several versions of grounded theory (GT) methods which have emerged since the original. McCallin (2004) suggests that three main versions of GT dominate, including the original version, Strauss and Corbin's (1998) more structured approach and Charmaz's (2006) constructivist version.

According to Charmaz (2006) GT is:-

'An inductive, comparative, and interactive approach to inquiry that offers several open ended strategies for conducting emergent inquiry'.

Strauss and Corbin (1998) suggest that:-

'GT examines the 6 'Cs' of social processes (causes, contexts, contingencies, consequences, covariances, and conditions) to understand the patterns and relationships among these elements'.

In GT methods, the researcher serves as both data collection instrument and analysis method and is trying to develop / induce theory. This starts with the process of coding which is iterative and non-linear. Strauss and Corbin's method divides the coding into three stages. Review of the original data line by line into codes that the researcher determines to be valuable is known as open coding. Axial coding involves combining original codes into major categories and defining subcategories and their relations to the majors (Developing themes and sub-themes) (Kendall 1999). Finally restricted

coding identifies the relationships among codes and categories. Constant comparison is key to the method, where data collection and analysis occur simultaneously and each datum is compared with every other datum (Cutliffe 2000). At times, one or more categories will be found to emerge with high frequency of mention and be connected to many other categories which are emerging. These are described as core categories.

Data saturation is achieved when additional data adds nothing to what you already know about a category, its properties and its relationship to the core category. The methods of coding and data analysis are slightly different in each of the versions of GT and it has been suggested that the Strauss and Corbin method is more of a science and the Glaser method is more of an art (Walker & Myrink 2006).

The fundamental components of a GT study include openness, analysing data immediately, coding and comparing, memo-writing, theoretical sampling, theoretical saturation and production of a substantive theory (Sbaraini 2011). The theory is dependent on context and never completely final (Charmaz 2006). GT has been criticised over the years, with suggestions that it oversimplifies complex meanings and constrains analysis (Thomas & James 2006).

Data Analysis

In this analysis, all goals were transcribed onto individual cards. Each patient goal was compared with the goals from previous and subsequent subjects. I used descriptive labelling for each of the common sets of data and this gave rise to themes and sub-themes (also know as categories and sub-categories) which summarise patient's views. Examples of these comparisons are demonstrated in figure 10.1.

Figure 10.1 Examples of comparisons

Example 1. ‘Reduce the number of times I go at night’, ‘to sleep through the night’, ‘better quality sleep’, ‘to get up less at night’ are all examples of patient set goals relating to nocturia, therefore these were sorted into a subcategory of nocturia and as it is one of the symptoms of OAB the core category was OAB

Example 2, ‘To go on journeys without worrying about toilet’,’ to take dog for a walk without needing the loo’, ‘watch a film without going to the toilet’, ‘complete a meeting at work without leaving to go to the toilet’ are all examples of patients goals relating to specific tasks that they wish to complete therefore each individual task was formed as a subcategory while the core category developed was related to finishing the task in hand.

Data saturation was achieved when further set goals could add nothing to what was already known about a category, its properties, and its relationship to the core category. Two researchers, myself and Carlos Curtis (a medical student wishing to gain research experience) independently performed the analysis and categorising of open ended goals and then discussions ensued to compare categories and agree terminology used.

Goal achievement was graded as follows: did not achieve, somewhat achieved, achieved, exceeded expectation and greatly exceeded expectation. Descriptive statistics were used to calculate goal achievement.

Baseline demographics of both studies

The baseline demographics of subjects are shown in table 10.2

Table 10.2 Baseline demographics and clinical characteristics

Variable	**SAFINA**	**Fesoterodine and SF**
Sex (N=)	N=331	
Male	68 (20.5%)	0
Female	263 (79.5%)	27 (100%)
Age (years)		
Mean	60.3	42.2
Range	23-86	20-73
Race, n %		
White	98.2	63
Other	1.8	37
Weight (Kg)		
Mean	79.9	78
Range	51-174	53.4-118
Duration since first diagnosis of OAB (yrs)		
Mean	7.7	4.6
Range	0.1-53.8	0.25-25
Incontinence, n (%)	39.9	81.5
Bladder diary variables per 24h, mean		
Micturitions	12.8	9.48
Nocturnal micturitions	2.7	0.93
Urgency episodes	9.1	4.93
UUI episodes	2.1	1.72

SAFINA Study – Results

The results of the nine fixed goals from the SAGA questionnaire can be found in the paper by Cardozo et al (2012). Of the 331 subjects who were assigned to treatment, 1137 open ended goals were set. The themes and sub themes that emerged from the data are listed in table 10.3 along with the number of patients expressing that subject as a treatment goal.

All goals were included in the analysis regardless of whether it was thought that these were unrealistic. Examples of what may be considered as unrealistic goals include ‘to not have any pain’, ‘to sneeze without leaking’, ‘to fully empty bladder’ and are discussed later in the chapter.

Table 10.3 List of themes and sub-themes from SAFINA study

	Theme **Goals related to :-**	**Sub-themes**	**Number**
A)	OAB	Reduce nocturia Reduce urgency Reduce frequency Reduce urgency urinary incontinence Reduce pain Not have to wear pads Reduce latchkey urgency	156 104 101 86 47 45 8
B)	Other LUTS	Reduce leakage on coughing Reduce leakage on exercising Empty bladder completely Improve weak stream Reduce leakage during housework Reduce leakage when swimming	41 23 22 8 4 3
C)	Finishing the task in hand	Car / coach journey without stopping Shopping trip without finding loo Walk dog Watch entire film / TV show / theatre Evening out for meal Finish activity (eg church service, football match, bingo, hair-cut. Visit family / friends Go on holiday Use public transport To queue without having to leave to go to the loo	78 56 52 49 40 37 29 19 16 2
D)	Psychological impact	To stop toilet mapping Reduce anxiety / embarrassment Feel in control Feel normal / confident To not smell To not plan life around bladder To enjoy what I am doing	75 21 18 15 8 6 3
E)	Work	Not leave meetings to go to loo To not keep leaving desk Complete an operating list To be more effective in role	14 7 1 1
F)	Sex	To have sex without needing the loo	2

Fesoterodine and Sexual Function Results

The results of the nine fixed goals and the correlation between the self-reported importance of a goal and the extent of their actualisation after 12 weeks can be found in Chapter 8. (Table 8.11 and 8.12)

Of the 27 patients who were assigned to treatment, 109 open ended goals were set. The themes and sub themes that emerged from the data are listed in table 10.4 along with the number of patients expressing that subject as a treatment goal.

Table 10.4 List of themes and sub themes from Fesoterodine and Sexual Function study

	Theme Goals related to :-	Sub-themes	Number
A)	OAB	To improve bladder control Reduce frequency Not have to wear pads Reduce frequency of the urgency Reduce nocturia To have warning time Reduce pain Reduce UUI	10 9 8 7 5 3 3 3
B)	Sex	To not leak during sex To be more sexually active with my partner No anxiety of leakage during sex Letting partner touch without worrying about needing the loo Better sex life including better orgasms	5 3 2 1 1
C)	Finishing the task in hand	Go out socially Go to market / shops without needing the loo Take part in sports activities Walk dog Go for long walks Use a cash machine without needing the loo	3 3 2 1 1 1
D)	Psychological impact	To stop toilet mapping Reduce anxiety / embarrassment To not smell To not plan life around bladder No stress To have peace of mind To have a happy and fulfilling life	4 2 1 1 1 1 1
E)	Other LUTS	To be dry Empty bladder completely Improve weak stream Reduce leakage on coughing Reduce leakage on exercising No urinary infections	3 2 2 1 1 1
F)	Being Free to	Drink whatever / whenever without needing the loo Go out without carrying spare underwear Leave the house without needing to pee beforehand Lie in bed when you wake up without rushing to the toilet Wear light trousers To be spontaneous	4 2 1 1 1 1
G)	Work	Not leave meetings / lectures to go to loo Complete work task eg clinic list, pool rotation without going to the toilet Not have to rush appointment to go to the loo	4 2 1

Discussion of themes

Although most of the themes identified in both of the analyses were the same, there was one additional theme identified in the Fesoterodine and Sexual Function (FesoSF) goals group that was not apparent in the SAFINA study group. There were also several differences in the importance of the themes between the two cohorts. The most common theme identified in both analyses was goals related to OAB symptoms.

OAB

In the literature, urgency has been described as the cardinal symptom of OAB (Cardozo et al 2009) and it is the only essential symptom when making the diagnosis (Abrams et al 2012). In a study by Coyne et al (2004) the experience of urinary urgency had a significant negative effect on HRQL and increased symptom bother more than incontinence, frequency, or nocturia. However, in the SAFINA cohort of patients the most commonly reported goal, listed by 47% of subjects was in relation to reducing nocturia episodes and only 31% of subjects listed reducing urgency as a treatment goal. In the FesoSF group only 18% of women were focused on reducing nocturia whereas 26% listed reducing urgency as a goal. This could suggest that in the SAFINA group, nocturia was their most bothersome symptom and this is in line with the baseline bladder diary variables with the SAFINA group reporting a mean number of nocturnal micturitions of 2.7 compared to 0.93 in the FesoSF group. It has been shown that the number of nocturia episodes per night is significantly associated with a reduced number of hours of sleep per night, reduction in QoL and sleep quality (Irwin et al 2008). Nocturia may lead to sleep insufficiency and consequently to a decrease in mental and physical health (Van Dijk et al 2004). For the SAFINA patients it was suggested that the impact of nocturia caused the largest disruption to their daily functioning, perhaps as a result of sleep deprivation. However, it has also been reported that symptom bother does not always correlate with

symptom prevalence and the most commonly reported symptoms may not be the most bothersome (Wang et al 2015); therefore, further investigation into this group is necessary to clarify.

The most common goal related to OAB set by 37% of women in the FesoSF group was related to improving bladder control. This was separated from urgency and UUI as it encompasses all the individual symptoms and implies an overriding mechanism to regain function.

Although 132 subjects in the SAFINA group reported incontinence only 86 (65%) of those added reducing incontinence episodes as a goal and only half of those reported wanting to no longer wear pads to manage their incontinence. In the FesoSF cohort, 85% reported incontinence, yet only 30% wanted to no longer wear pads. This is surprising as incontinence and the need to wear pads is often described as a major cause of impaired quality of life and a driver for patients to seek help. In a study by Anger et al (2011) women with severe OAB attended focus groups and discussed their symptoms and treatment options. One of the themes that emerged was that incontinence pads were the only management strategy that provided the women with the freedom to participate in and complete activities without the worry of leakage which would result in the need to change clothes. Anxiety is often linked with OAB symptoms and it may be that for many of the OAB wet patients, wearing pads can help reduce anxiety as it is commonly adopted as a coping strategy, containing the problem. Pad use can also be a security measure or a learnt behaviour so women continue to wear pads even if their incontinence has resolved. This study did not record whether patients had reduced the size of the pads that they wore or the number used throughout the day but this could be an interesting area of investigation.

It is also interesting to note that 47 patients in the SAFINA group and 3 patients in the FesoSF group wanted to reduce pain associated with their symptoms. Hanno et al (2009) explored the relationship between bladder pain syndrome and whether the sensation of urgency can overlap with the symptom of pain. They suggested that it is likely that the urgency

experienced by these patients is different from that described by patients with OAB and in this cohort of patients their description of wanting to reduce pain could be in relation to pressure symptoms causing discomfort.

Other lower urinary tract symptoms

This was the second most common theme in the SAFINA trial but only the fifth in the FesoSF trial. Under this theme, in both cohorts, four of the sub themes were all in relation to reduction of leakage during different activities eg during coughing, exercising and during housework. This type of leakage is generally associated with SUI but can also be attributed to provoked detrusor contractions. In the SAFINA study, patients recruited reported OAB symptoms but patients with urgency predominant mixed symptoms were also included. There were no UDS performed to demonstrate the presence of DO or USI. Therefore it is not possible to differentiate between these groups in this analysis as to aetiology of the urinary leakage. In the FesoSF study, although urodynamics were performed, the numbers are too small to reliably determine aetiology. In reality, it is unlikely that all these episodes of leakage are caused by an involuntary detrusor contraction and therefore these are not realistic goals for patients in this clinical trial. It could be suggested that when these goals were discussed with the clinician, a further conversation may have been warranted to clarify whether these symptoms were clinically more stress related and if so patients should have been advised why it is unrealistic to expect symptom resolution from the therapy they received. Additionally a discussion about alternative treatments that they could be offered for these symptoms could then be undertaken.

It could also be construed as unrealistic for patients to list ‘to empty bladder completely’ as a goal in these studies. It is an accepted side effect of fesoterodine that approximately 7% of patients will experience the symptom of incomplete bladder emptying whilst taking the medication. During the screening phase in both trials, all subjects underwent assessment of post void residual and anyone with a significant residual volume was excluded from the trials therefore bladder emptying should not have been a problem

for these groups of patients. It could however, be considered by some patients that they were not emptying their bladder completely as a surrogate measure of bladder "irritability", if for example, the patient felt that she needed to void ten minutes after having just emptied her bladder. However, this would usually result from their OAB causing after contractions and possibly poor fluid habits rather than the bladder not emptying completely. It should also be noted that the SAFINA study included men and the analysis did not differentiate the men's goals from the women's. LUTS including storage and voiding symptoms eg slow stream, and incomplete emptying are common in men and can be related to benign prostatic enlargement (Abrams et al 2013b). This may account for why this theme was far more prevalent in the SAFINA study compared to the Feso and SF group.

Finishing the task in hand

This was the third most common theme in both of the studies and one that had not been identified in the literature. It highlights the frustrations in daily life that many patients with OAB suffer. Not having to interrupt what they are doing in terms of travel, social life, and every day chores are common goals that patients aspire to achieve from therapy and these vary minimally between the cohorts. A third of all the patient goals in the SAFINA study were in relation to being able to complete everyday tasks without having to worry about their bladder. This disruption of daily life has also been reported in a study by Irwin et al (2005) who found that 76% of individuals reporting OAB symptoms stated that the condition interfered with or made it more difficult to perform daily activities. Most clinicians treating OAB patients treat the symptoms. However, for the patients it is not always the symptoms they specifically want to change but the impact of the symptoms on their daily life. For many subjects completing a simple task such as taking the dog for a walk without needing the toilet or being able to watch a film without interruptions is what they would like to achieve from therapy. Interestingly the SAGA tool captured these issues and should allow more focused treatment based on these concerns. It is important to remember these motivations when planning treatment and providing bladder retraining etc. as

individualised management to work towards. Thus allowing the patient to complete the tasks, most important to them, which may ultimately increase satisfaction and fulfil expectations and improve quality of life.

Psychological

It has been reported that patients with OAB experience higher rates of depressive symptoms (Irwin et al 2005, Coyne et al 2008b). In a series of interviews with patients with OAB symptoms, interviewees expressed constant anxiety and worry about finding and reaching a toilet in time to prevent urine leakage and some reported anxiety that constantly needing to go to the toilet created feelings of hopelessness and depression (Nicolson et al 2008). Those feelings of anxiety were mirrored in this analysis with many subjects wanting to reduce the anxiety in relation to their bladder, to stop worrying about finding a toilet and just to feel more in control of their bladder and consequently their lives. Studies have shown that improvement of urinary incontinence can improve self-esteem (Hagglof et al 1998).

A recent systematic review by Sakakibara et al (2013) assessed the literature relating to bladder dysfunction in patients with anxiety and depression. They found that depression / anxiety was an obvious risk factor for OAB and presumed that this reflected that the bladder is under emotional control. They suggested that ameliorating bladder dysfunction is an important target in treating patients with depression/anxiety. However, equally these psychological symptoms could lead to anxiety and depression due to the impact of OAB on the patient's life. This study did not assess the numbers of patients suffering anxiety and depression and whether their bladder symptoms caused the anxiety and depression or conversely whether their anxiety and depression caused their bladder dysfunction. Previous work by Parsons et al (2004) reported that simply the need to attend a specialist gynaecology clinic places a significant psychological burden on women and this should also be considered as a potential source of anxiety.

A common goal in both cohorts of patients was ‘to stop toilet mapping’. This is a form of coping strategy where patients plan their journeys / activities / shopping by the location of available toilets (Ness 2012). It is not uncommon for a patient to decline visiting new places for fear that they will not be able to find an appropriate toilet in time. It has been recognised as an issue and there are now toilet maps online for many town centres and Apps where one can track the location of the nearest toilet as well as special access keys to help overcome this barrier.

Several patients in each cohort also reported fears in relation to not smelling of urine. It has been demonstrated that women who are afraid of the odour of urine are increasingly likely to seek medical help for their UI (Hagglund et al 2003).

Work

This theme is similar to those set out in the finishing the task at hand theme but the impact of bladder symptoms on work productivity has been studied. According to Irwin et al (2005) men are more likely than women to worry about the impact that OAB can have on their work life including worrying about interruption of meetings which was identified as an issue by subjects in both studies. Also this can be a major factor in deciding the type of work or timing of retirement. A study assessing the impact of UI on women in the workplace reported a negative impact on concentration, performance of physical activities, self-confidence or the ability to complete tasks without interruption (Fultz et al 2005). For younger patients, as seen in the FesoSF study, it also correlates to concerns of being able to sit through lectures and academic studies without having to leave to go to the toilet.

Sex

There have been many studies that show the negative impact of OAB on SF (Salonia et al 2004, Milson et al 2009). These papers suggest many different reasons for this effect including embarrassment, fear of CI on penetration

and orgasm, loss of confidence, fear of smelling, loss of libido. However, in the SAFINA study only 2 subjects reported goals in relation to SF. It has also been suggested that concerns about time constraints, lack of effective treatments and embarrassment may prevent women initiating a discussion about sexual concerns with their doctors (Kingsberg 2006). According to O'Donnell et al (2005) only 24% of women are not at all embarrassed to discuss sexual problems with a doctor in comparison to 87% when discussing allergies or cold/flu, and approximately a third of women would not initiate a discussion about sexual issues with their doctors (Coyne et al 2007). The very small number in this sub group could suggest that the clinician reviewing the goals with the patient did not broach the subject of SF with the subjects at the time of screening and goal setting and as the literature would imply that patients will rarely disclose this information without prompting.

This suggestion would appear to be likely as in the FesoSF cohort, sex was the second most common theme with several subthemes related to leakage during intercourse, frequency of sexual activity and anxiety related to potential leakage and needing to void during intercourse were also noted. Given that the primary outcome of the FesoSF study was related to SF, the clinician had already initiated the discussion on the topic and the patients would have also completed two questionnaires specifically concerned with SF prior to completing the SAGA questionnaire so this may have helped the women to verbalise their concerns and hopes in this area without embarrassment.

<u>Being free to …..</u>

This is another novel theme that only emerged from the FesoSF patients and focuses on the fact that women do not want to feel constrained by their bladder symptoms or have to prepare for everything. Some of the sub themes relate to coping strategies to manage bladder symptoms e.g. carrying spare underwear, voiding 'just in case', fluid restriction, while some relate to constraints caused by anxiety / leakage where women will only wear

dark coloured trousers in order to hide any possible accidents or the desire to be spontaneous.

Perhaps the most interesting sub theme is ‘to drink whatever / whenever without needing the loo’. It could be considered that this is an unrealistic goal as even for women with ‘normal’ bladder function, if they drink large volumes of certain fluids they will need to pass urine regularly and frequently; however, it would be unusual for them to report symptoms of urgency or UUI. In situations like this patient education regarding normal and abnormal bladder function is helpful in the establishment of healthy bladder habits (Wyman et al 2009).

This theme and also the ‘completing the task at hand’ theme provide new insights into the impact of OAB on women’s quality of life both physically and psychologically and are worthy of greater exploration. Many QoL tools used in routine practice focus on the symptoms associated with OAB and minimally on role limitations as a result of symptoms. This could raise questions regarding the validity of the questionnaires given the findings presented here as they may be missing important factors. However, the International Consultation on Incontinence Questionnaire Overactive bladder quality of life (ICIQ OABqol) does appear to address some of these issues as it asks questions relating to journey planning, social activities, planning activities and toilet access. Further investigation of this concept and the available QoL tools is recommended.

Overall, the goals of the patients in each study were fairly similar in relation to themes and sub themes, however the prevalence of themes varied between the two studies. This could potentially be due to the way in which the questionnaires were introduced and completed or due to the mixed cohort of patients in the SAFINA study compared to only female patients in the FesoSF study. There may also be differences dependent on the other questionnaires that were completed at the same time which may provide inspiration for treatment goals or suggest something to aspire too. This is

likely to be the reason that more patients set goals related to SF in the FesoSF group compared to the SAFINA group.

SAFINA Goal Achievement

A total of 251 subjects completed the trial and goal achievement was ranked for all goals set out by subjects and the level of achievement of their personal goals is listed in table 10.5 Approximately half of the patients in this trial achieved their goals following 12 weeks of therapy, with a further third somewhat achieving their goals.

Table 10.5 Achievement of Goals SAFINA study

Level of Achievement	**% of subjects**
Did not achieve	18.7
Somewhat achieved	32
Achieved	32.5
Exceeded / greatly exceeded expectation	16.8

Feso and SF Goal Achievement

Of the 27 women enrolled, 20 completed treatment. When considering overall goal achievement in the FesoSF study only one subject did not achieve her goals with a further 35% somewhat achieving their goals. 60% of subjects achieved their goals with 40% of those exceeding or greatly exceeding their expectations. Table 10.6 demonstrates the breakdown of goal achievement.

Table 10.6 Achievement of goals FesoSF study

Goal Achievement	% of subjects
Did not achieve	5
Somewhat achieved	35
Achieved	20
Exceeded / Greatly exceeded expectation	40

A greater percentage of patients achieved their goals in the FesoSF study than in the SAFINA study overall but given the vast differences in the numbers of patients in each study it is not possible to compare this in greater detail. It is however noted that the baseline severity of OAB symptoms was greater in the SAFINA population and this may account for the variation of goal achievement.

Limitations

There are several limitations to the data presented and discussed in this chapter. Firstly, in both studies not all patients originally enrolled in the trials completed the studies, so complete data are not available for all participants. It is recommended that the SAGA questionnaire is completed by the patient with the clinician. Given that there were 39 different sites recruiting subjects for the SAFINA study, there may be variation in the level of involvement of the clinician at each site and this can introduce a risk of bias in the goals set. In areas where clinician involvement was minimal this could account for some patients setting unrealistic goals and ultimately negatively affect goal achievement. In the FesoSF study only one clinician worked with the patients on their SAGA questionnaires so there is uniformity in the level of involvement, however, this in itself could be an area of potential bias as the clinician could inadvertently lead the patient to certain goals.

It should be noted that both of the studies discussed have slightly different inclusion / exclusion criteria and a large difference in patient numbers so due to the smaller numbers in the Feso and SF group, it may mean that the themes were less well defined and that they were not a directly comparable group.

The main limitation of this data is in the methods used for analysis. The grounded theory approach uses a thematic analysis to generate a theory from the data. As previously noted, the fundamental components of a GT study include openness, analysing data immediately, coding and comparing, memo-writing, theoretical sampling, theoretical saturation and production of a substantive theory (Sbaraini 2011). However, it is recognised in this case that a thematic approach to the analysis of the data was used but this was not taken to the next stage by which a GT was produced.

There is a limitation in the format of the questionnaires as there is limited space for patients to express their goals and this may reduce what they are wanting to say. Another limitation with the use of the questionnaires is that is does not provide any opportunity for probing of those goals or for understanding the thoughts and feelings associated with them, limiting the text base for analysis. This is a recognised limitation of questionnaire derived qualitative data (Atieno 2009). Ideally individual patient interviews or focus groups should be used to allow for indepth probing of these goals.

In routine practice and the clinical trial setting the SAGA questionnaire is designed to be completed by the patient with the clinician, however, this is more to ensure that the open ended goals set are feasible and realistic rather than deep and meaningful. It could be questioned whether these are a true expression of patient goals for example if patients were unable to think of specific goals at the time it is difficult to know if they were prompted with responses or if these were really what mattered to them. According to Beiske (2002) open-ended goals / questions have the advantage of offering a wide range of responses that help to capture the flavour of people's answers, while not influencing the outcome of the question by pre-

determining possible responses however, answers are often difficult to evaluate and tend to vary in clarity and depth.

The SAGA questionnaire also has a section of fixed goals (the results of which were presented in Chapter 8). Yet this may be even more limiting in understanding patients goals from treatment as fixed goals / questions assume a general knowledge / experience that patients may not experience or have a different understanding of based on personal perception which may be influenced by age, culture, education etc (Beiske 2002).

Given these limitations, it could be questioned whether the use of this questionnaire in practice is really good enough to understand patients goals from treatment. However, it is not feasible to perform and analyse in depth interviews with all patients receiving treatment for OAB and at present there are no other alternative tools available.

Conclusions

In this chapter I have described a thematic analysis of two data sets. This revealed common themes but also showed that there were some differences. The new themes that emerged from this data was ‘completing the task in hand’ and ‘being free to ..’ which have highlighted how for many patients their treatment aims are more focused on completion of tasks and preventing restrictions on everyday life rather than a specific reduction in a particular symptom. This emphasised the impact that symptoms can have, and disruption that they can cause to their everyday activities.

The most significant difference noted between the studies is the number of goals related to sexual function. For many women these were very important goals but they needed the introduction regarding the topic and discussion with the researcher to encourage them to think about these and list them as treatment goals. This highlights a practice recommendation that when

HCP’s provide counselling and discuss symptoms, goals and treatment outcomes, SF and the impact on this should be introduced by the HCP and included in the discussions based on the patient’s agreement.

Chapter 11

Additional Research Questions Methodology

Introduction

During the course of the main trial described previously, significant problems arose with recruitment of sexually active (SA) women with overactive bladder (OAB) into the study. At several time points in the study, questions were raised to try to investigate why recruitment was so poor and to understand if it was a problem with the study sites, the methodology, or the sample population.

Advice was sought from clinical and academic supervisors, the principal investigators at each of the other study sites and from experts in the field. The other clinicians reported that many women who they saw in clinical practice were not sexually active (NSA) or did not meet the inclusion criteria. They also commented that some women had not wanted to discuss sexual function (SF) with the clinical teams when approached (especially the male study staff) or did not wish to complete personal questionnaires.

Despite changes to the methodology (previously discussed in chapter 9) by updating and expanding the inclusion criteria, recruitment rates did not improve and it became clear that our knowledge of the prevalence of SA in the study population was lacking. It was also noted that although many women attending clinics in the unit report OAB, a lot were NSA for a variety of different reasons. At this point the question raised was 'What is the prevalence of SA in women with OAB?'

To answer this question and to help understand the recruitment problems in the main study, it was decided to perform an investigation of the whole clinical population at the index site. This was designed to gain insights into the prevalence of SA in women with OAB and other LUTS and to understand why women are not sexually active. The findings of this investigation are discussed in Chapter 12.

It was also noted by the investigators that there was a group of women who did not wish to talk about their SF or enter a trial related to sexual outcomes. It has already been noted in chapter 7 that the recruiting clinicians were not asked to follow a standardised approach when taking a sexual history from women or discussing recruitment into the trial and that this would be a potential recommendation for future research. However all of these concerns noted raised issues with communication and how women were identified and approached. This led to the formulation of a further research question – "How do women want to be approached about the topic of SF?" It was considered that if the research team could understand how best to initiate discussions regarding SF with women then potentially it would break down some of the barriers and help the team to develop enhanced communication skills to improve the recruitment process.

In a bid to understand these communication issues, Chapter 13 details the findings from two focus groups for women with LUTS who attended the Urogynaecology outpatients department for assessment and treatment. The aim of these focus groups was to understand how women want to be approached regarding the topic of sexual function along with any barriers they have encountered and what their preferences are regarding when the conversation should be initiated and by whom.
This chapter details the methodology, research tools, and plans for analysis used to investigate these additional research questions identified.

Research Question 1

What is the prevalence of SA in women with OAB attending a London Urogyanecology outpatient service?

To answer this question and to help understand the recruitment issues in the main study, it was decided to perform an investigation of the whole clinical population at the index site. This was designed to gain insights into the

prevalence of SA in women with OAB and other LUTS and to understand why women are NSA.

Objectives

The primary aim of this investigation was to assess the prevalence of SA in our OAB population. The secondary aims were to evaluate why women were not sexually active (NSA), to assess if this was bothersome to them, to evaluate variations in SA according to UDS diagnosis and to compare questionnaire responses between the SA and NSA groups.

The Research Tool

In the healthcare setting, one way of trying to improve screening of certain conditions is to use validated questionnaires that can be completed by the patient in private, prior to consultation and used by a clinician to prompt further dialogue if the questionnaire suggests that this is necessary. At the start of this thesis, there were no validated questionnaires to assess SF in women who were NSA.

In 2013, the IUGA Sexual Function Working Group conducted a re-evaluation of the PISQ, enhancing the ability to assess outcomes in women who are NSA (Rogers & Pons 2013b). They noted that the original framework of the PISQ questionnaire had not included women without a partner or those who did not consider themselves to be SA and it was recognised that this may underestimate pelvic floor dysfunction (PFD) impact on SF since women with severe PFD may elect to become sexually inactive (Rogers et al 2013a). They published the Pelvic Organ Prolapse/Incontinence Sexual Questionnaire, IUGA-Revised (PISQ-IR) to aid clinicians to assess SF in women who were and were not SA.

The PISQ-IR consists of two sections. Section one is completed by women who are NSA and consists of six questions to understand reasons why they are NSA and their feelings / degree of bothersomeness of their sexual status.

Section two is completed by women who are SA (with or without a partner) and consists of fourteen questions incorporating sexual response, partner related issues, condition specific issues and assessment of satisfaction / feelings in association with their sexual lives.

Methods

It was decided to screen SF in all women attending our one stop UDS clinic. In our clinical practice this is the service that all women reporting LUTS would be triaged to following referral to the department. All women attending the UDS clinic at KCH were sent the PISQ-IR (a copy can be found in the appendix) as part of the pre-visit information pack that also contains a three-day bladder diary and the KHQ. These were collected and reviewed when the women attended for assessment. Initial analysis was performed using descriptive statistics and recorded in association with demographic data and UDS diagnosis.

Data Analysis

Following this, the statistician used a multivariate binary logistic regression to analyse the risk of being SA as a function of potentially contributing factors identified in the PISQ-IR. All factors were entered as covariates in the initial model via a forced entry method. The resulting model's goodness-of-fit was determined using the Hosmer-Lemeshow statistic. The proportion of variance in the occurrence of SSIs explained by the model was analysed using the Nagelkerke's R2.

The analyses were performed three times to investigate the whole cohort of women and two specific sub-groups relevant to the main CTIMP: -

1. All women attending the UDS clinic
2. Only women diagnosed with DO following UDS
3. Only women complaining of OAB symptoms with normal UDS parameters

It is acknowledged that in the main study, all women with OAB or DO were included and for many of the outcomes assessed as one group. However, for this study the decision was made to separate these into two groups to understand if there are differences between the groups related to prevalence or sexual activity even though none were identified from the outcomes in the main study.

The results of this investigation and ensuing discussions are presented in Chapter 12.

Research question 2

How do women want to be approached about the topic of SF?

In a bid to answer this research question and gain insights that may benefit routine clinical practice and future research studies, it was decided that a qualitative approach to data collection would be the most appropriate. According to Hammarberg et al (2016) qualitative methods are used to answer questions about experience, meaning and perspective, most often from the standpoint of the participant. The most common methods of data collection in qualitative research are interviews, focus groups, observation and action research. It was decided that observation and action research were not suited to the research question as we wanted to understand women's views about the approach to SF, not just how it was performed. In depth interviews would have provided us with a lot of information about women's individual opinions and experiences. However, individual interviews are associated with a considerable time, manpower and cost implication (due to transcription etc). Focus groups are more suited when there is limited time / manpower, however, it was also thought that greater insights would be developed by the group dynamics as we were trying to develop ideas for future changes to approach that would be suitable for all. Based on this, two focus groups for women with LUTS who attended the Urogynaecology outpatients department for assessment and treatment were

undertaken. The aim of these focus groups was to understand how women want to be approached regarding the topic of sexual function along with any barriers they have encountered and what their preferences are regarding when the conversation should be introduced and by whom.

The role of Focus Groups

The development of Focus Groups (FGs) originates from an interview technique called focused interviews described by Merton & Kendall (1946). Powell et al (1996) define a focus group as:-

'A group of individuals selected and assembled by a researcher to discuss and comment on, from personal experience, the topic that is the subject of the research'.

Kitzinger and Barbour (1999) suggested that FGs are commonly used as a tool for exploring people's views or perceptions of, attitudes towards and experiences of particular areas in life. According to Breen (2006) FGs can also complement and further explain statistical information obtained from other evaluative processes.

In the 1990's, FGs gained popularity as a method of collecting data through group discussions particularly in social science and medical research (Hyden and Bulow 2003). While one to one interviews allow researchers to obtain individual attitudes, beliefs and feelings, focus groups can elicit a multiplicity of views and emotional processes within a group context and a larger amount of information can be gained in a shorter period of time (Gibbs 1997).

The crucial feature of a focus group is interaction as it enables the participants to ask questions of each other and re-evaluate their own understandings of their specific experiences (Kitzinger 1995). However, in any group situation, there is also the potential for dominant voices, normative discourses and conflict and contradiction (Smithson 2000). It is the

responsibility of the researcher / moderator to promote debate by asking open questions and probing for details, move things forward when the conversation has reached a conclusion and ensure that the conversation stays on course, as well as manage any conflict and ensure that all participants are actively involved in the discussions.

A focus group generally involves 4-8 participants, too many and it is not always possible to add richness and depth to the conversation, to few can stall the conversation and result in a lack of opinions and views and data saturation will not be achieved (Wilkinson 1998). As discussed in Chapter 9, data saturation is only achieved when additional data adds nothing to what you already know about a category, its properties and its relationship to the core category.

FG's are not only beneficial to the researcher but can also have benefits for the participants. Goss and Leinbach (1996) reported that the opportunity to be involved in decision making and to be valued as experts can be empowering for many participants. However, some participants may also find them intimidating and unenjoyable experiences.

Aims / Purpose of focus group

To explore with women their thoughts and feelings about being approached to discuss sexual function

Overall Goal

To generate ideas, for the purpose of devising recommendations for future change and improvement in clinician's approach to discussing SF.

Methodology

Following a review of the literature (as part of the initial study and additional investigations undertaken), I had the opportunity to discuss practicalities and

problems with a researcher (Dr Angela Grainger) whose own PhD methodology was qualitative and incorporated FGs. I was encouraged to write down what information I expected to gain from the FGs and what I planned to do with the information to help guide the development of the questions to be asked. My expectations incorporated several different facets of the previous investigation findings and are set out below.

What I expect to get out of this investigation:-

1. An insight into the variation of patients experiences in current practice in relation to assessment of SA and their perceptions on the appropriateness / effectiveness of this so that current practice can be examined and a need for change identified

2. An understanding of how women want to be approached on the topic of SA / SF when attending outpatient urogynaecology clinics so that clinicians can be educated and act in line with patients wishes

3. An awareness of the barriers that patients feel prohibit or restrict their ability to discuss SF as they would wish to so that communication difficulties can be addressed and environmental issues / service structure changes can be considered to overcome these

4. An understanding of the patient's perceived role of the clinician and factors that encourage / impede discussion regarding SF to enable assessment of staffing in the service and develop appropriate training / communication skills dependent on clinician and patient needs

<u>Sample population</u>

To ensure that all the women attending the focus group had appropriate personal experience, they were all recruited during or following attendance at the Urogynaecology department at KCH. This meant that all the women

would have undergone some form of assessment of LUTS / POP and as part of routine care and been approached about SA by a member of the multidisciplinary team. It was thought that a combination of new patients and long term patients would be ideal to elicit current and previous practice as well as reassessment of SA and differences in approach dependent on the HCP who the patient was seeing.

Considerations with the planning and implementation

Two FGs were undertaken during different weeks and at different times of day. The dates were set based on room availability as well as my own availability. One was organised for the middle of the day so that women with children at school would be able to attend and not miss the school runs. The other was organised in the evening so women who worked a '9-5' job would be able to attend after work and negate the issue of needing leave to attend during work hours. To encourage participation an incentive of a £50 Marks and Spencer's gift voucher was agreed and an invitation letter including a brief description of the process, the times of the FGs and details of the incentive was developed (included in the appendix).

Invitation letters were sent to potential women with their appointment letters for UDS clinics and bladder retraining group sessions, other invitation letters were handed to women by reception staff when booking follow up appointments and invitation letters were also left on the tables in the waiting areas and posted to the inside of toilet doors for the women to read. If interested in attending the FG, women were asked to either let us know in person when they attended the clinic, email me or my colleague, or telephone the department (on a number with answerphone capabilities) to provide their name, contact details and preference for which FG they would like to attend.

Following expression of interest, a formal patient information sheet on the process, including why the research is important, what is expected of them and the fact that the discussions would be recorded was provided either in

person, electronically by email or a hard copy in the post dependent on the patients preference (A copy of the PIS is included in the appendix).

The FGs took place in the hospital, but not in the clinical department. However, patients were asked to meet in the main waiting area of the department as this is a point that they all knew in the hospital and once the group had assembled they were led to the alternative meeting area. Refreshments in the form of cold drinks, fruit and biscuits were provided and in view of patients presenting complaints the room booked had accessible toilet facilities located nearby. All the women sat round a table with myself at one end to moderate and the scribe sat amongst the women.

On arrival, the women were asked to complete a consent form (included in the appendix). This also allowed for collection of demographic data to ensure that the groups were homogenous. Demographics of the participants is discussed in Chapter 13.

Both of the FGs were recorded onto a Dictaphone and transcribed but there was also a scribe in the room at the time to note down salient points, comments, behaviours identified. The same individual scribed for each of the FGs and typed up her notes by the following day to ensure that they remained fresh in her memory.

I acted as the moderator in both of the FGs and immediately after each session wrote memos reflecting on comments, feelings, behaviours, how the participants responded to the questions and language used. These memos and the scribe's notes were then used in the analysis.

The first FG was counted as a pilot study and opinions were sought from the scribe regarding how she though the questions came across, whether my level of involvement in the conversations was appropriate and whether the structure of the FG needed to be revised. Two of the participants were also seen by myself in a clinical setting the week after and I was also able to gain opinions from them regarding their experience of the FG.

FG interview schedule

To ensure consistency across the FGs an interview schedule was developed. It included a welcome to all the women and an introduction to myself, the scribe and the clarification of our roles. Following this I provided the participants with an overview of the topic and how the research questions had been developed. I went on to describe their role in the session and confirmation of confidentiality. Ground rules for FG etiquette including only talking one at a time, being respectful of other people's opinions and allowing everyone a chance to vocalise their opinions were set.
A variety of questions were posed to the groups. Although the starting questions were the same in both sessions, as the moderator dependent on the direction of the conversation, the order of the following questions was changed if I felt it would further encourage an area of discussion. All questions were posed to the two groups.

Ethical considerations

During the set up and development of the FGs, several ethical considerations were identified and potential strategies to mimise the impact of these developed. It was hoped that by making the FG an informal process, in a different area of the hospital it would help put the participants at ease. The availability of refreshments allowed for a short period of informal conversation prior to the start of the FG which it was hoped would help to establish a rapport amongst the participants.

For some of the women I had actively been involved in their assessment and management in practice. It was especially important for them to understand that I wanted to know both the positives and negatives of their experiences and ensure that they would be comfortable providing the information in order to avoid biasing the discussions. The assurance of confidentiality helped towards this.

Considerations of how to manage individuals if they were too aggressive in their opinions or disrespectful of others were deliberated and a plan was also put in place of what additional support / advice women could be offered if concerns were raised that were causing personal distress. This included a further assessment in the outpatient's clinic, referral to the psycho-sexual counselling team, or to the safeguarding team if issues of domestic violence or abuse were discovered.

Data Analysis

In this study, GT methodology (as previously described in chapter 10) was used to analyse the data. On this occasion, I performed the coding and generation of themes from the transcripts of each FG and from memos written directly after the FGs. Following this a second independent researcher without knowledge of this field of investigation analysed the data, then a discussion ensued to compare categories and agree terminology used. Member checking was performed by some of the participants when they came back to clinic appointments following the FGs and by an expert in the methodology. Member checking is defined as a quality control process by which a researcher seeks to improve the accuracy, credibility and validity of what has been recorded during a research interview (Harper & Cole 2012).

In addition to the individual coding, the data were uploaded to NVivo 11 (a qualitative data analysis computer software package) to help sort, search and arrange the information and examine relationships in the data. Following the analysis of the data, a further literature search was performed to discover whether any further research had been undertaken that would illuminate further understanding of the data uncovered in my research.

The themes and Sub themes that emerged from the data and discussions related to these are presented in Chapter 13.

Conclusions

This chapter defined the rationale and methodology of two research questions that were developed from the identification of limitations in our original methodology that may have hindered recruitment to the main study. The results presented in the next two chapters will address these limitations and inform future studies.

Chapter 12

What is Sexual Activity and how prevalent is it?

Introduction

One of the challenges identified with recruitment into the main trial was related to a lack of sexually active women attending the department. As previously noted in chapter 11 this led to development of a new research question - What is the prevalence of sexual activity (SA) in women with overactive bladder (OAB) attending a London Urogynaecology outpatient service?

To answer this question and to help understand the recruitment issues in the main study, it was decided to perform an investigation of the whole clinical population at the index site. This was designed to gain insights into the prevalence of SA in women with OAB and other LUTS and to understand why women are not sexually active. This chapter presents and discusses the findings of this investigation.

Methods

The full methodology was discussed in chapter 11. The analyses were performed three times to investigate the whole cohort of women and two specific sub-groups relevant to the main CTIMP: -

1. All women attending the Urodynamics (UDS) clinic
2. Only women diagnosed with detrusor overactivity (DO) following UDS
3. Only women complaining of OAB symptoms with normal UDS parameters.

An overview of the significant results is presented in this chapter, however, the full results for each group are available in the appendices.

Results

Four hundred questionnaires were completed over 9 months. This does not represent all the women attending the UDS clinic. Twenty two women (5%) refused to complete the questionnaires because they did not feel it was appropriate or did not want to discuss the subject. Some women were unable to read or write in English and although the PISQ-IR is available in different languages it was decided not to further investigate this group as they would not have been suitable for the main trial. A further group of approximately 50 women 'forgot' to complete or return the questionnaires at their appointment. This is not uncommon in routine clinical practice. Table 12.1 displays the presenting complaints of the women who completed the questionnaires.

Table 12.1 Presenting complaints of Group 1

Complaint	**Number of women (%)**
Urinary Incontinence (UI)	193 (48)
Pelvic Organ Prolapse (POP)	34 (9)
LUTS and POP	117 (29)
Other (eg recurrent UTI, voiding difficulties)	56 (14)

Group 1

Of the women assessed, two hundred and thirty two (58%) were SA and one hundred and sixty eight (42%) were NSA.

Three hundred and sixty three women went on to have a full urodynamic assessment. There was minimal difference in SA activity between the different UDS diagnoses as shown in Table 12.2. UDS were not performed if the patient had a symptomatic UTI or if it was felt to be unnecessary for their further management.

Table 12.2 Sexual activity according to UDS diagnosis

Urodynamic Finding	N	% SA	% NSA
Test not performed	37	35	65
Normal	128	55	45
Mild urodynamic stress incontinence	35	68	32
Moderate urodynamic stress incontinence	30	60	40
Severe urodynamic stress incontinence	20	75	25
All urodynamic stress incontinence	85	67	33
Detrusor overactivity	95	60	40
Voiding difficulties	4	50	50
Low capacity	26	62	38
Urodynamic mixed incontinence	21	70	30

Eighty nine (53%) of the NSA women were NSA because of lack of a partner. When the 79 women who were NSA but had a partner were asked to consider the reasons why they were NSA, 60% reported that this was secondary to their bladder symptoms, 45% due to other health problems, 53% reported having no interest and 58% were bothered ‘A lot’ by their lack of sexual activity.

Group 2

Ninety five women were found to have DO on UDS. Of these, 60% (n=57) were SA. Of the SA women 93% (n=53) reported symptoms of UI compared to 100% of the NSA women.

For 47% (n=18) of the NSA group, lack of a partner was cited as the reason they were not SA. Only 9 women reported having a partner and the other women did not answer. When the 9 women who were NSA but had a partner were asked to consider the reasons why they were NSA only 33% (n=3) reported that this was secondary to their bladder symptoms, 55% (n=5) due to other health problems, 67% (n=6) reported having no interest and only one woman was bothered 'A lot' by her sexual status.

Group 3

Sixty seven women reported symptoms of OAB but had normal UDS findings. Of these only 45% (n=30) were SA. Of the SA women 87% (n=26) complained of OAB wet compared to 70% (n=26) of the women who were NSA.

65% (n=22) were NSA because of lack of a partner. Only 6 women reported having a partner and the other women did not answer. When the 6 women who were NSA but had a partner were asked to consider the reasons why they were NSA 67% (n=4) reported that this was secondary to their bladder symptoms, 83% (n=5) due to other health problems, 83% (n=5) reported having no interest and 50% (n=3) were bothered 'A lot' by their sexual status.

The differences in baseline characteristics between the three groups is presented in table 12.3. The differences in rationale for sexual inactivity between the three groups is demonstrated in table 12.4

Table 12.3 The differences in baseline characteristics between the three groups.

	N	Mean age (years)	Median parity	Sexually Active	Not Sexually Active	Concomitant POP + LUTS
Group 1	363	45.06	2	58%	42%	38%
Group 2	95	49.74	2	60%	40%	32%
Group 3	67	49.65	2	45%	55%	37%

Table 12.4. The differences in rationale for sexual inactivity between the three groups

Group	N=	Sexually active	Not sexually active				
			Lack of partner	With a partner			
				Due to bladder problem	Due to other health condition	No interest	Bothered 'a lot' by sexual status
1	363	58%	53%	60%	45%	53%	58%
2	95	60%	47%	33%	55%	67%	11%
3	67	45%	65%	67%	83%	83%	50%

Comparisons of the SA and NSA populations

Several analyses were performed to attempt to compare the SA population to the NSA population in each group. There were no factors identified that would make someone more likely to be SA than NSA. There were no differences in feelings of frustration, anger and sexual inferiority between women who were SA and those who were NSA.

To further investigate feelings of anger and frustration in the SA group, the patients were broken down into smaller groups according to their presenting complaint of either UI, POP or both. Although, women with UI or POP reported similar levels of anger and frustrations, it was the women with UI and POP who were the most frustrated and angry with the impact that their condition has on their sex life. This is demonstrated in table 12.5.

Table 12.5 Breakdown of frustration and anger in the SA group according to presenting complaint in comparison to the NSA population (Group 1)

Question	**Urinary Incontinence (UI) alone (%) (N=112)**			**Pelvic organ Prolapse (POP) Alone (%) (N=17)**			**UI and POP (%) (N=89)**			**Not Sexually Active (%) (N=168)**		
	A	**D**	**U**	**A**	**D**	**U**	**A**	**D**	**U**	**A**	**D**	**U**
I feel frustrated by my sex life	43	52	5	35	59	6	61	36	3	38	38	24
I feel angry because of the impact that UI/POP has on my sex life	42	53	5	47	47	6	57	39	4	31	38	26

A= agree, D= disagree, U= unanswered

An evaluation of the relationship between sexual status and avoiding / restricting sexual activity through fear of leaking urine and / or stool and / or a bulging in the vagina was not significant. However, 43-73% of women report that fear of leakage caused them to avoid or restrict SA and this was also a particular concern in those women without partners.

Assessment of the NSA population

A detailed analysis of the NSA group was performed using a binary logistic regression to try to explore factors that could influence reasons for sexual inactivity such as age, parity, UDS diagnosis along with all the answers to questions 2 and 3 on the PISQ-IR. None of the co-variates made a significant contribution.

Assessment of Bothersomeness

Bothersomeness of sexually inactivity (Question 6) was examined to understand if it is age dependent or related to the reason for not being SA.

Group 1

The relationship between bothersomeness and age was analysed using an independent T-test. In group 1, this showed that those who were not bothered were, on average, 10.46 [95% CI: 4.861, 16.068] years older than those who were bothered ($t(126) = 3.696$, $p < 0.000$). There were no relationships identified in group 2. In group 3, it revealed a significant difference in the mean age, with those who were bothered being, on average, 12.3 years (95% CI: 1.05-23.55) younger than those who were not ($t(28) = 2.240$, $p = 0.033$).

A Binary logistic regression was used to investigate the relationship between bothersomeness and factors identified in Q2 among the NSA group (the rationale for sexual inactivity ie due to bladder problems, other health conditions, lack of interest). In group 1, bothersomeness was associated with

lack of interest in SA and being NSA due to UI/FI/POP problems. No relationships were identified in group 2 or 3.

Assessment of the SA population

Examination of the SA group was performed to determine if factors such as age, parity and UDS diagnosis impact upon SF.
A Binary logistic regression was used to investigate the relationship between questions 7,9, 10, 11 and 18 and co-variates among the SA group.

Group 1

Q9 (leakage of urine and or stool with any type of sexual activity)
The model was statistically significant $\chi2(10) = 29.525$, $p = 0.001$. It explained 18.5% of the variance in sexual activity correctly assigned 62.6% of cases. Patient reported symptom of UI was the only covariate that significantly contributed to a person's likelihood to leak with any type of sexual activity. The model parameters are displayed in table 12.6.

Table 12.6 Factors influencing urinary leakage during SA

	B	**SE**	**Wald**	**df**	**Sig.**	**Exp(B)**	**95% C.I.for EXP(B)**	
							Lower	Upper
Age	-.010	.014	.469	1	.49	.990	.964	1.018
Parity	.608	.446	1.86	1	.17	1.838	.767	4.404
Prolapse	-.364	.346	1.10	1	.29	.695	.353	1.369
UI	1.45	.479	9.27	1	.002	4.298	1.681	10.98
FI	21.0	17889.5	.000	1	.99	1455331225.	.000	.
UDS - USI	-.086	.422	.041	1	.839	.918	.401	2.098
UDS - DO	.514	.427	1.45	1	.228	1.673	.725	3.859
UDS - VD	.872	1.144	.581	1	.446	2.391	.254	22.51
UDS - CAP	-.380	.657	.334	1	.563	.684	.189	2.479
UDS - Mixed	-.276	.623	.196	1	.658	.759	.224	2.571
Constant	-1.1	.695	2.79	1	.09	.313		

The relationship between Q9 and UI was further investigated through a Pearson's Chi Square test. This showed that those reporting UI were significantly more likely to leak with any type of sexual activity than those without UI ($\chi2(1) = 14.211$, $p < 0.000$). It is interesting to note in this analysis that 39% of women reporting UI, never leak with any type of SA.

Of the 232 sexually active women 22 were SA without a partner. For those with a partner 37% reported that their partner some / most or all of the time had a problem that limits their SA. In general 70% felt that their partner had a positive effect on their sexual desire and 65% stated that their partner had a positive effect of the frequency of SA. However, being SA does not guarantee satisfaction with 59% women reporting that they sometimes / usually or always want more from their sexual encounters.

The relationship between Q18 and Prolapse was further investigated through a Pearson's Chi Square test. This showed that those with POP were 2.5 times more likely to avoid sex through fear of bulge /leaking than those without ($\chi2(1) = 8.339$, $p = 0.004$) and is reported in Table 12.7.

Table 12.7 Factors causing restrictions on SA

	B	**SE**	**Wald**	**df**	**Sig.**	**Exp(B)**	**95% C.I.for EXP(B)**	
							Lower	Upper
Prolapse	1.131	395	8.222	1	.004	3.099	1.430	6.716
Parity	.445	.427	1.084	1	.298	1.561	.675	3.607
UI	.442	.456	.937	1	.333	1.555	.636	3.802
FI	20.157	17659.5	.000	1	.999	567646277.673	.000	.
UDS - USI	-.656	.453	2.099	1	.147	.519	.214	1.260
UDS - DO	-.260	.431	.363	1	.54	.771	.331	1.797
UDS - CAP	.881	.740	1.41	1	.23	2.414	.566	10.30
UDS - MUI	.555	.855	.421	1	.51	1.742	.326	9.310
Constant	-.152	.435	.121	1	.72	.859		

Group 2

The model was not significant for any of the questions.
Of the 57 SA women 6 were SA without a partner. For those with a partner 25% (n=14) reported that their partner some / most or all of the time had a problem that limits their SA. In general 74% (n=42) felt that their partner had a positive effect on their sexual desire and 67% (n=38) stated that their partner had a positive effect of the frequency of SA. However, being SA does not guarantee satisfaction with 60% (n=34) women reporting that they sometimes / usually or always want more from their sexual encounters.

Group 3

Q9 (leakage of urine and or stool with any type of sexual activity)

The model was statistically significant $\chi 2(4) = 14.405$, $p = 0.006$. It explained 49.4% of the variance in sexual activity and correctly assigned 74.2% of cases. Having at least one live birth made a significant contribution, resulting in a 42-fold increase in the chances of urinary incontinence during sex. However, the mode of delivery was not assessed in this group.

The model was not significant for questions 7, 10, 11 and 18.

Of the 30 SA women 2 were SA without a partner. For those with a partner 20% (n=6) reported that their partner some / most or all of the time had a problem that limits their SA. In general 93% (n=28) felt that their partner had a positive effect on their sexual desire and 90% (n=27) stated that their partner had a positive effect of the frequency of SA. However, being SA does not guarantee satisfaction with 43% (n=13) women reporting that they sometimes / usually or always want more from their sexual encounters.

In summary, these analyses showed that more women with OAB are NSA compared to the other UDS findings, yet women with POP are more likely to avoid sex. Younger age, lack of interest and being NSA due to bladder and

bowel problems are predictors of increased bothersomeness of sexual inactivity. Parous women with OAB are 42 times more likely to experience CI than nulliparous women with OAB.

Discussions

What is sexual activity?

According to Rogers et al (2018) the assessment of sexual activity status should be self-defined and not limited to women who engage in sexual intercourse, as such, in the 2018 IUGA / ICS joint report on the terminology for the assessment of sexual health of women with pelvic floor dysfunction there is no set definition for SA. The PISQ-IR was developed by the same clinician and on discussion with Dr Rogers, she reported that they did not define SA on the PISQ-IR as they purposely wanted patients to self-assess SA in line with their own opinions. However, this is likely why there was such an issue with item non-response.

When trying to find a definition for SA, the free dictionary online defines it as ‘activities associated with sexual intercourse’. The medical dictionary as ‘an activity that is sexual in nature’. The sociology dictionary as ‘a general term for sexuoerotic interactions with oneself and/or others’ and the urban dictionary as ‘fluid exchange’.

Different types of sexual acts or behaviours are well defined in the literature eg vaginal intercourse, anal intercourse, masturbation but no standardised definition of SA could be found. To further investigate this and ensure that the researcher was not missing evidence, I had the opportunity to meet with Dr Goldstein, Past President of the International Society for the Study of Women's Sexual Health and current Editor in Chief of Sexual Medicine Review, and ask questions related to defining SA. He stated that he was not aware of a set definition of SA but in his unit and practice in clinical trials

related to SF, they use the definition set on the Female Sexual Function Index (FSFI) questionnaire (previously mentioned in chapter 2). According to the FSFI:-

'Sexual activity can include caressing, foreplay, masturbation and vaginal intercourse. Sexual intercourse is defined as penile penetration (entry) of the vagina. Sexual stimulation includes situations like foreplay with a partner, self-stimulation (masturbation), or sexual fantasy.'

This is a far more inclusive list and defines certain sexual acts or behaviours which would potentially change the responses of many of the women who previously defined themselves as NSA. However, it is still inadequate as in this definition sexual intercourse only includes penile penetration of the vagina and not oral, anal or urethral intercourse with alternatives such as fingers or sex toys.

The FSFI definition also has a time stipulation associated as it only asks about activities in the past four weeks. Time restrictions have been previously discussed as a barrier to the identification of accurate prevalence figures and it could be questioned whether 4 weeks is too short a time frame for assessment.

Ultimately, this lack of a standardised definition of SA and standardised time frame for assessment, presents a fundamental challenge in any future research into sexual function in women as the population is never accurately described. This will either lead to challenges in recruitment as seen in this study as women may think they are NSA when actually they are, or potentially patients who think they are SA (when if you go by the FSFI definition are not) and this may lead to inaccuracies in the trial outcomes. Therefore, the most pressing recommendation from this thesis is for a review and standardisation of terminology related to SA.

Prevalence of SA

This investigation has clarified the observations noted by the team in practice regarding the lack of suitable women to recruit into the main study as 42% of the women attending our UDS clinics are NSA and 55% of our OAB population are NSA. This number is slightly higher than other studies that have reported sexual inactivity rates among women attending hospital clinics between 28.4-40% (Rosen et al 1993, Moreira et al 2006, Addis et al 2006). However, community studies have reported the prevalence of sexual inactivity as high as 49% (Lutfey et al 2009). The difficulty with interpreting these numbers is the lack of standardisation of time scales. This study just asked if women were currently SA, some of the studies assessed SA in the last four weeks and some in the last year, hence variations may occur. The study reporting the high figure of 49% was only including those women who were NSA in the past four weeks so figures may be lower if a longer timescale was adopted.

In this cohort, women with DO are the most likely to be NSA due to lack of a partner and the least likely due to their bladder and bowel problems. They are also the least bothered overall about their lack of SA. The women in the OAB group appear to be the most likely to restrict SA due not only to their bladder and bowel problems, but also their other health conditions. Lack of interest ranged from 53-83% among the groups. Lutfey et al (2009) found that 60.8% of women were NSA due to lack of a partner and 51.5% due to lack of interest, in their community study. They reported that only 4.1% were NSA due to UI, however, this is because it was an assessment of all women in a community setting rather than a biased view of women referred to a hospital setting with a urogynaecological problem.

It is important to remember when discussing the prevalence of SA in this cohort that it is a biased group of women as they have all made the move to seek help for a UI or POP problem, which is why they had been referred into the clinic. There are many women in the community who have not sought

help for a variety of different reasons and then the impact of UI / POP on their SF remains unknown.

Prevalence of OAB

In the initial trial feasibility discussions, it was documented that 50% of our clinical population reported OAB symptoms and would potentially be suitable for the study, however, in this investigation, only 40% of the women attending the UDS clinic were found to have OAB / DO. This may have also negatively affected recruitment in the main trial but it is important to remember that the women attending this clinic were only the new referrals and not women who had previously been investigated, therefore there was also a population of women attending the outpatients clinics for bladder retraining and medication reviews who may have been suitable for the trial but not included in this investigation, hence the variation in figures.

Identifying factors

There were no factors identified in this study to help understand who may and may not be SA. This is not unexpected as SA is dependent on more than just age, parity and UDS diagnosis but is also under the influence of a wide range of external and internal factors such as religion, personal beliefs, family / cultural influences, education, availability of a sexual partner, views of peers and these were not considered in this study (Wight et al 2006, Villarruel et al 1998, DeLamater & Sill 2005). For many of the women, the rationale is also multifactorial.

Bothersomeness of sexual status

The most clinically important findings from the examination of the NSA group is in relation to bothersomeness. Those who reported no interest in sex, were 5 times more likely to be bothered by their sexual status and those who reported being NSA due to their bladder / bowel / prolapse condition were nine times more likely to be bothered by their sexual inactivity.

This bothersomeness or level of personal distress is one of the factors that differentiates a sexual dysfunction from a sexual problem that does not significantly affect a woman's sexual life or sexual satisfaction (Bancroft et al 2003, Dennerstein et al 2005). Ferenidou et al (2008) assessed SF and satisfaction in women attending hospital appointments for any medical condition other than a sexual problem. They found that the most bothersome sexual problem, reported by 17.1% of women was 'little or no interest in sex'. However, it was also the condition that women are least likely to seek help and treatment for. Other studies have reported the rates of low desire in women as 10-41% (Lewis et al 2010).

The highest level of personal distress is seen among women who are NSA due to their UI / POP. It has long been noted that sexual avoidance is common among women with UI, with reports of up to two thirds of women in one cohort avoiding SA, particularly in those under 65 years and unmarried women (Norton et al 1988). Other studies have reported avoidance of SA due to prolapse as 13.9% and due to fear of incontinence as 14.9% (Knoepp et al 2010). This high level of personal distress is likely to be due to the psychological impact of UI / POP on SF. Roos et al (2014) studied women with UI and POP to determine what women perceive to be the real problem with FSD and stated that 'women with POP had a negative image of their vagina, which caused them to be insecure about their partner's sexual experience, while women with UI were embarrassed about their incontinence and pad use, and feared smelling of urine'. These issues can lead to sexual avoidance and inactivity.

As women with partners who are NSA due to their UI/POP have indicated the highest level of bother, this group warrants a particular focus and may benefit from referral for psychosexual counselling as well as appropriate management of the UI / POP. For the women who are NSA without a partner further discussions are warranted to understand whether their bladder condition / POP is hampering their desire to find a partner and causing additional anxiety regarding future sexual relationships, thus

preventing them from being SA should they chose to be, if it is not related to their reason for being NSA.

The degree of bothersomeness in the NSA group was found to be age related. The average age of the NSA group in the whole population was 54.9 years and those who were least bothered by sexual inactivity were found to be 10.46 years older on average. In the OAB population, the average age of the NSA group was 54.5 years and those who were most bothered were on average 12.3 years younger. Shifren et al (2008) performed a study to estimate the prevalence of self reported sexual problems and the extent of personal distress in women and found that the prevalence of distressing sexual problems peaked in middle-aged women (45-64 years) and then decreased with age which would fit with the picture of older women being less bothered. There are many suggested reasons for this including the effect of the menopause, however, the mid-life and later life can also be times of partnership transitions via separation and divorce or be associated with changes in employment and financial status that may affect SF (DeLamater & Karraker 2009). For some it may also be a time when they are assuming a care giver role or confronting illness or death and priorities change and all of these may impact upon sexual activity.

Fear OF Leakage

Although only 36-38% of the SA women reported leakage during sex, 61-77% of the SA women (and 48-68% of the NSA women) avoided SA for fear of leakage. As expected the diagnosis of UI was significantly associated with this. In the OAB population, parous women are 42 times more likely to leak during sex than nulliparous women. However, the fear of leakage appears to be more problematic than actual leakage itself. This is also reflected in the study by Kneopp et al (2010), where only 9% of women reported leakage during SA but 14.9 reported avoiding SA for fear of leakage. Fear of leakage can affect a woman's motivation to be SA, her arousal and ability to achieve

orgasm and if she contracts her pelvic floor to prevent leakage can lead to dyspareunia (Roos et al 2014).

Impact of POP

It is interesting to note that women in the SA group with POP were 2.5 times more likely to avoid SA than others. POP had a negative impact on a woman's body image (Jelovsec & Barber 2006). According to Novi et al (2005) women with POP were more likely to report negative emotional reactions associated with sex and a significantly higher rate of avoidance of SA due to embarrassment compared with controls. These high avoidance rates were also seen in the study by Tok et al (2010) and would fit with the findings in this cohort. However, there were only a small number of women in this group (N=17), therefore further investigation with a far larger number of women with POP alone would be necessary to confirm or dispute this finding. Recent work by Jha et al (2016) reported a study with 343 women undergoing surgery for POP or SUI and compared the effect of each of these conditions on SF. They found that women with POP (79% vs 36%) and their partners (50% vs 24%) were more likely to avoid SA than those with SUI, which mirrors the findings in this study.

In this study women with UI and concomitant POP reported the highest levels of anger and frustrations with their sexual lives. This would fit with work previously published by Ozel et al (2006) who found that women who had UI and POP had significantly poorer SF than those with UI alone. In clinical practice particular focus should be made to ensure that sexual problems are addressed as part of routine clinical care for these women.

Satisfaction from sexual activity

A significant proportion of women (43-60%) were not always satisfied with their SA. Those with DO were the most satisfied while the OAB group were the least satisfied. There could be a multitude of reasons for this. For those women with POP, patients have reported the sensation of obstruction within

the vagina and vaginal laxity as two of the main reasons for reduced sexual satisfaction (Srikrishna et al 2008). It has also been observed that there is a significant interaction between communication and sexual satisfaction (Litzinger & Gordon 2005, Montesi et al 2013, McNulty et al 2016), and that these interpersonal factors play a major role in maintenance of sexual problems (McCabe et al 2010) yet marital satisfaction and communication with partners was not addressed in this study. Pascoal et al (2013) performed an exploratory study to understand how lay people define sexual satisfaction and identified two themes. The first was in relation to sexual pleasure including arousal, orgasm and sexual openness, the second theme emphasised relational dimensions including romance, expression of feelings and mutuality and that both areas are crucial to sexual satisfaction.

Schoenfeld et al (2017) also reported that husbands positive interpersonal behaviour towards their wives improved sexual satisfaction. Again, this was not addressed in our study so it is not possible to attribute the cause of these high sexual dissatisfaction rates. According to Rehman et al (2013) women tend to be more sexually satisfied if they are older, in a stable long term relationship, are more erotophilic (respond to sexual cues in a positive manner) and have better sexual and non-sexual communication with their partner.

Overall, the women with OAB symptoms but normal UDS variables report the lowest levels of SA, report the most bother and the least sexual satisfaction and a greater number of them report other health conditions that also impact upon their sexual function. It could be suggested in this group that women with OAB may have other concomitant pathologies such as urogenital atrophy and psychological factors that are impacting upon SF rather than just bladder pathology. It could also be considered that these women are more aware of physical symptoms or less able to manage psychological symptoms as they present with similar symptoms to other women but with increased bother. Further research into this group of women is needed to improve our understanding and guide future treatments.

Reliability and Validity of the PISQ-IR

It was noted that 87 (52%) of the NSA and 83 (36%) of the SA group did not complete every question in the relevant section of the questionnaire. Most commonly in the NSA group – if they did not have a partner they did not go on to complete the rest of the questions in the section. Item non-response has been noted in previous work considering the scoring and development of the PISQ-IR (Rockwood et al 2013). They also found that item non-response was higher in the NSA group ranging from 5-33% but low in the SA group (up to 7%). The scoring was adjusted to allow for this, however, the rates of item non-response are far higher in this 'real world' study. This could reflect our patient population, for example some may have felt that the questions were not relevant to them or they may not have wanted to disclose sensitive information. It could be suggested that the clinician reviewing the patient and collecting the questionnaire should have gone through the answers in more depth and encouraged the women to answer all the questions. However, the aim of this study was to assess prevalence of SA among the women attending the unit and although women were given the opportunity to discuss SF with the clinician as is the normal practice, particular attention to the answers of each question were not discussed during the consultation unless the patient specifically requested. Alternatively, the high non-response could just be a sign of questionnaire burden as these were sent to the patients at the same time as a KHQ and a three day bladder diary so it may have been too much to complete prior to their visit to the department.

Several comments were made by patients regarding the questionnaire that may explain some of the non-response, as they did not feel that there was a suitable option that explained their situation. It was felt that all the reasons for not being sexually active were quite negative (no partner, pain, due to bladder / bowel problems). Several women attending were Virgo Intacta through choice to wait until marriage and felt that there was no suitable reason for them to make comment. Also, many women reported that although they were in a loving relationship, their partner had health issues causing erectile dysfunction and this was the reason for not being sexually

active, but this option was also not available on the questionnaire. On further questioning several of the NSA women reported being intimate with their partners without vaginal penetration yet they felt this counted as being NSA despite the SA section allowing for women not having intercourse. As previously noted at the start of these discussions, a sentence regarding what is considered as sexual activity may prove beneficial for women completing this questionnaire in the future.

Given all the limitations and non-response noted, this study questions the validity of the PISQ-IR in practice. In its simplest form, validity is the ability of an instrument to measure what it is intended to measure. If the aim of the PISQ-IR is to assess in the first instance whether women are sexually active or not, then based on the fact that there is no definition of SA and the concerns noted by women above in relation to this, it is not a valid tool in our population. This is contrary to the validation studies performed by Rogers et al (2013), where testing on 589 women provided baseline data and 200 post treatment confirmed content, and criterion validity and responsiveness. The paper reports that 31 interviews were also conducted regarding the content of the questionnaire and this number is noted as being limited but it does claim that data saturation was achieved. It does not mention in the paper any concerns over defining SA as raised by the cohort under investigation in this study.

With regard to the reliability of the tool, the Rogers (2013) paper also assessed and confirmed the item distribution and test-retest reliability of the PISQ-IR. The challenge when considering the test retest reliability of this tool, is in the very nature of the topic under assessment. Sexual activity is a continuum and often changes over time for a variety of reasons not only due to health status but a variety of other factors. Within the reliability assessments, the second questionnaire was sent out 3-6 months after the first and there is the potential for many of the women to change their SA status. Interestingly, unlike the FSFI, the PISQ-IR does not set any time frames within which SA may have occurred, so there is the potential for a variety of different responses and time frames that women may establish

themselves when completing the questionnaire that may impact on its reliability. This is however, an inherent issue for any questionnaire potentially assessing SA, where a time frame has not been set.

This study has raised the question about the role of the PISQ-IR in routine clinical practice. It may help us to gain a deeper understanding of a patients SF, which may help clinicians to understand which patients are most troubled by sexual problems and tailor assessment and therapy to meet their needs. However, without the clinician actively reviewing it with the patient it could become just another paper exercise. It may therefore be better used in women who report a sexual problem when questioned instead of as a screening tool for all women in clinics.

Conclusion

Overall this study provided us with a lot of useful information about our clinical population. Although a high proportion of them were NSA, which confirmed our difficulties with recruitment to the main studies, we were unable to find any specific factors that were more likely to lead to sexual inactivity. It did however, enhance the knowledge regarding the level of distress or bothersomeness experienced by people who are NSA due to their UI / POP and the need for further research into this area to understand the mechanism behind the problems and how they can be resolved. The validity of the PISQ-IR has been questioned and it has highlighted the fundamental need for standardised terminology defining SA for any future research.

Chapter 13

How do women want to be approached regarding sexual activity?

Introduction

A key limitation for recruitment that was identified in the main trial was regarding communication and how women were identified and approached to enter the trial. This is described in chapter 9 with study sites reporting that they did not always ask women about SA or that women had been reluctant to discuss SA with certain health care professionals. A recommendation was made for a standardised approach to discussing SA for future studies. However, there is no precedent for this in the literature or recommendations for best practice. Ensuing discussions led to development of a new research question:-

'How do women want to be approached about the topic of SF?'

To investigation this research question, two focus groups (FG) were run with women who had attended our department with Urogynaecological problems. The full methodology for this investigation was described in Chapter 11. This chapter will report the themes and subthemes that emerged from the focus groups and discuss their implications in clinical practice and future research methodology.

Findings

Description of participants

In total, 7 women attended FG1 and 5 attended FG2. There were meant to be six women in FG2 but one cancelled just before the session started as her train to the hospital had been cancelled so she would not make it on time.

The youngest participant was 27 years and the oldest was 75 years. Half of the women were in the 41-60 age range. In relation to ethnicity, 8 were Caucasian, 3 Afro-Caribbean and 1 Asian. Three had been referred to the department with SUI, six had OAB / DO, two had POP in isolation while 3 of

the women with SUI / OAB had concurrent POP. The final woman had been referred with recurrent UTIs.

Parity ranged from 0-4 live births. Half were post-menopausal. A quarter of the women did not report any co-morbidities but the others had 1-3 each. Co-morbidities included hypertension, asthma, hypo / hyper thyroidism, COPD, inflammatory bowel disease, mental health complaints, and neurological conditions. The patients had been under the care of the department for a wide range of time from one month to 18 years. 7 of the women were SA and 5 NSA.

Two of the women were unemployed, three were retired, and the others worked in retail, administrative / clerical work, teaching and health care. The demographics of the participants is set out in table 13.1.

Table 13.1 Demographics of the participants

Patient No	**Age**	**Diagnosis**	**Parity**	**Referral date**	**Co-morbidities**	**Occupation**
1	53	SUI/POP	2	01/2017	1	Retail
2	46	DO	0	2003	1	Office
3	61	POP	2	02/2017	1	Retail
4	53	DO	1	2008	2	Unemployed
5	73	POP/OAB	1	2010	2	Retired
6	67	DO	0	2002	0	Retired
7	54	SUI	1	11/2016	0	Health care
8	40	POP	3	2008	1	Teacher
9	42	OAB	0	2010	1	Clerical
10	27	RUTI	0	04/2017	1	Unemployed
11	43	DO/POP	4	04/2017	0	Housewife
12	75	SUI	2	1989	3	Retired

Core themes

There were three core themes that emerged from the data. They were:-

1. Perceived barriers to discussions on sexual function
2. Communication factors
3. Ideas to introduce the discussion

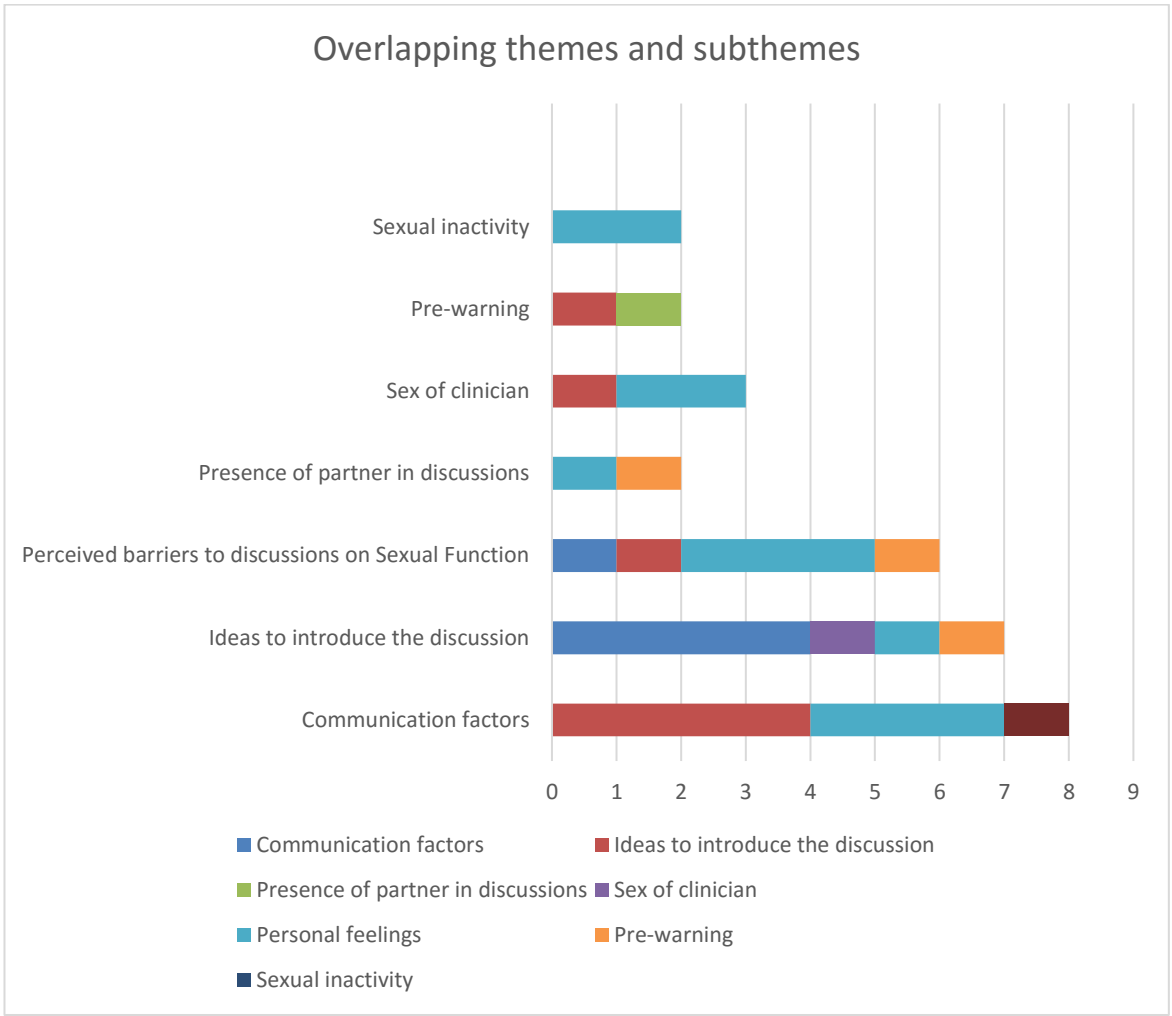
Each of the core themes had sub themes identified as demonstrated in table 13.2.

Table 13.2 Themes and sub themes identified

Number	Theme	Sub theme
1	Perceived barriers to discussions	Sexual Inactivity Sex of the clinician Presence of a partner Age of clinician Family dynamics Timing of discussion Woman centred Cultural issues Environment
2	Communication factors	Methods of communication Personal feelings What if we don't ask
3	Ideas to introduce the discussion	Written methods Conversation starters Pre-warning

There was considerable overlap between some of the themes and sub themes and this is demonstrated graphically in Figure 13.1.

Figure 13.1 Overlapping themes and subthemes



1. Perceived barriers to discussions about SF

One of the strongest threads running through the data was related to the factors that women perceived to be barriers to discussions about SF. Some of these barriers were common to several of the women in the group and others were very individual perceptions. There was no one barrier identified that all women were in agreement about.

Sexual Inactivity

It seems quite contradictory that sexual inactivity is seen as a barrier to discussion of SF. However, there were several reasons identified that supported this subtheme. For some women who were NSA, the rationale for this was cut and dry so that further discussion would be halted.

'Mine is through choice after my husband passed away 25 years ago and I don't like to talk about it'

However, for others, being NSA raised questions about their own relationships and lifestyle that they were unable to answer because they do not understand themselves.

'When I go to the doctor and he asks me why I am NSA, I don't know the answer to give him because I don't know why I am'

For several of the women, just because they were NSA at that time, they did not want the conversation to stop there. They reported feelings of exclusion and they are missing something:-

'I don't want to be excluded because I am NSA at the time I am being asked the question'
'That's why I think discussing a patient's sex life, whether or not they are having it, not having it, want it, why, is very important; otherwise it is a bit like we are being put out to grass'

For these women it was highlighted that just because they are NSA at that time, does not mean that they are not seeking a relationship, and that in

reality there are a whole different group of concerns and issues that women have in new sexual relationships, that they may have liked to discuss further with the clinician.

'I don't have a partner at the moment, but one of my concerns with the next one is I am embarrassed, whereas my old partner didn't care because he knew'

Sex of the clinician

For nine participants in the FGs the sex of the clinician was deemed to be a significant barrier to the discussion of SF. All of these women expressed concern that they felt happier talking to a woman about SF and all agreed that there were increased feelings of embarrassment and personal discomfort / distress when the conversations were had with men. This preference for a female clinician was not dependent on whether the women had children, however, it was the younger women who did not share the views of the majority of the group. Comments included:-

'You want to die really…you feel happier with a woman, it's not really something that you want a man to see'
'I think also that if it's a woman or a man asking you makes a difference. I think you would be much happier telling a woman than a man'

'Just make sure it is a woman and not a man as I think you would just be embarrassed saying that to a man'

'You feel more comfortable with a woman'
'I just think that if a man asks you that, you just straight away have that sort of embarrassment with a man, whereas, if a woman asks you, I think you feel that bit more comfortable'

For the other three women who were not worried about the sex of the clinician, they were more focused on other traits of the clinicians that they felt to be important such as:

'*That you are comfortable with the person'*
'That there is consistency with who you see'
'As long as they are experienced and know what they are talking about, then that makes me feel confident'

However, when talking further about experience it was agreed by the groups that when it came to discussion SF it was not necessarily the consultants who they thought to be the experts and that again sex of the expert was important.

'I know that consultants are specialists, but if they are male, you are not going to get the answers you need as much as if you have a nurse who was specially trained to sensitively deal with that aspect'

Presence of a partner

Another significant barrier discussed by the FGs was the presence of a partner in the consultation. Only one woman reported that she did not have a problem discussing SF in front of her partner as they had a very open relationship and were happy talking about such issues. For all the other women, even those who did not currently have a partner, it was felt that having a partner with you during the discussion would prevent women from being completely honest. For some this was because the partner was not aware of issues and they didn't want them to be voicing comments such as:

'Even with your husband sitting there, who you are obviously intimate with, I think a lot of people would not be comfortable talking about their issues with sex with their husband, with their husband sitting there, and more so if it is just a friend'
'The last thing I would have wanted to discuss would have been our sex life with him sitting there'

'I think you have to keep the romance alive a bit: they don't need to know everything'

'He doesn't need to know everything that's going on down there. He needs to look at that and feel good'

One of the participants told the group about the lengths that she goes to, to hide the bladder problems that she has had for 20 years from her husband and the impact that it has had on their sex life. She went on to reveal the excuse she gives her husband when her tries to get intimate.

'My husband hasn't a clue that I am terribly incontinent because I avoid sex; it's awful, but I have to wear a pad 24/7 and it's just dripping wet. I avoid it and I sleep right on the side of the bed, but I put it down to, he's got a defibrillator, so I don't want him to die! I don't talk to him, I can't'

Some of the women felt that their partners were either uncomfortable being in those discussions or in some cases disinterested:

'It's something they don't want to delve into'
'My husband said that he didn't feel comfortable coming'
'My husband wouldn't be interested at all'

It was felt by the groups that the scale of the barrier may be dependent on the length of the relationship with several women feeling that in long term relationships it would be less of an issue than for someone in a new relationship.

Age of clinician

Along with issues surrounding the sex of the clinician for many of the participants in the FGs age was also a significant barrier to discussions. Many of the women reported experiencing increased embarrassment discussing SF with younger clinicians and felt that slightly older clinicians conveyed more empathy and understanding. It was also believed if the clinician in question was too good looking it impaired discussion. Women considered that:

'I would feel more comfortable discussing it with a 65 year old guy than some Greek God, tanned, sitting opposite me; I could not meet their eye and discuss anything'

' I think that with age does come a bit more empathy and understanding; not necessarily, but I think that I would feel much better happier discussing things of a sexual nature, with someone who is not a young pup, for want of a better word. Just because life brings about experiences, so for me age is just as important as gender'

'I wouldn't be happy telling a 25 year old, I would be embarrassed. I would blush. I would be embarrassed'

'I have seen different boys; and they were boys; I'm not saying I'm that old, but they were just boys'

Some of the group actually felt that young age was an advantage in the discussion as it may make the discussion more open.

'I think the younger people might be more open to talk about that sort of thing'

Many of the participants discussed the training of the junior doctors surrounding SF and suggested that in order for them to gain a deeper understanding of the personal discomfort that patient's experience they should:

'Make them go through the questions; make them be the other person so they know what it's like. As part of training, I think that would be valuable, because they would know that it is uncomfortable'.

<u>Family dynamics</u>

The way in which women's views were formed on the barriers to discussions was often linked to their family dynamics. Some of the women who appeared to be more open minded and liberal with the discussion, reported very open relationships with their family on the topic of sex, whereas for some, previous family experience seemed to add to their own barriers and beliefs. Two of the very contrasting views included:

'My daughter is 19 and my son is 18 and their sex lives are completely different to mine at that age. My daughter is as happy with a girl as a guy and is very experimental. With both of them, nothing is off limits; nothing is taboo. Their friends are all the same and they are very open and are not embarrassed to talk about it; I'm very fortunate like that'

'When I was young, nobody talked about anything like that. When you had your period, it was your curse; you did not talk to your mum about anything like that. My mum told me about sex when I was 11. With my children now, if I say anything about it they tell me to shut up because they can't bear it!'

Timing of discussion

There were mixed feelings within the group as to when is the ideal point in a consultation for the discussion of SF to be initiated. Some felt that it was often asked as a final point towards the end of a discussion and that took away some of the importance of the discussion. They also felt that the clinicians didn't really want to get into the discussion. Others were not concerned where in the conversation it took place as long as it happened. However, everyone was in agreement that it should not be at the beginning of a consultation, unless that was the presenting complaint. The length of time that people had for the discussion was also linked into this and concerns were raised that it was not something that can be rushed and this does not always fit into short time frames especially such as those in general practice clinics. Some of the remarks included:-

'It's making sure perhaps that the sex doesn't come last, it's in the middle, so there's not that thing about, "oh, just before we finish…" however you decide to ask the question, because otherwise it makes it look like it's a bit peripheral and it's one of those out of the door things'

'I leave it to the Consultant whenever they bring it up; as long as they have brought it up, I do want them to address it, I don't mind if it's at the beginning or the end'

'With my GP, if I know they are 10 minutes I have to book a double appointment; I can't do it in 10 minutes'

Woman centred

It was recognised by the groups when listening to each person's opinions that the topic and reaction to discussions on SF are very different for everyone. Not all patients can be grouped into certain categories and even though certain ways of discussion work better for some, this is still not right for everyone. This subtheme indicates the recognition of woman centred individualised care and that no one approach is going to be acceptable for everyone. This is supported by the following comments:-

'I think as well that it does depend on the individual. What you can say to one person you can't say to another. I mean we can talk quite nicely here, but it is not for everybody. I don't know how you could group everybody in…it's impossible'

'You should ask them how they would like to be - we can tailor it to you'

Cultural issues

It was surprising to note that only one participant made reference to religious beliefs being a barrier to discussing SF. All of the cultural references in the FGs were in association with the age of the women and the differences in the 'culture of youth' compared to the older generation. It was felt that the younger women were more confident discussing SF and less embarrassed but also that sexual practices were changing and that this may also be impacting upon differences in the ages.

'I speak to younger women and it seems that sex is becoming a bit of a performance art now, rather than just being intimate and enjoying something with somebody'

'I think that the younger you are, possibly the more open you are…well not open, but the more confident you might feel'

'Because of my age, years ago we didn't talk about things like this'

Environment

The environment within which the discussion takes place was believed to have an impact on the discussion by many of the participants. From a physical environment perspective, women wanted to talk in a room and not a cubicle and wanted it to be secluded to ensure privacy. They wanted a clinician who was going to put her at ease and had a gentle approach.

'Tucked out the way'

'I don't want it to be in a cubicle, it's got to be in a room'

'They have got to make you feel at ease. If you've got someone who is really officious, treating it like a school exercise, you are not going to feel as comfortable as someone who is kinder, has the gentle approach'

'Having someone who is quite friendly and not too many people and just having a nice environment so that I feel comfortable'

One of the concerns raised by several of the women was that often when coming to busy clinics you are seem by different clinicians each time and they do not know your history and you have no rapport with them and this can be a barrier to discussion.

'I always see a different person and I feel like no-one cares I sometimes think "Am I just a number".

'If I got a different person every time I wouldn't like it'

The presence of medical students in the consultation also garnered mixed reactions from the women. Some felt that it was difficult enough having the conversation with one person let alone two or more whereas one found the presence of a student enhanced her own experience of the consultation.

'I certainly don't want a room full of people. If I'm knocked out unconscious you can do what you want, but when I'm there and I'm fully aware…'

'At my last appointment there was a student there and in actual fact it was good, because she was thoroughly explaining everything to the student, so it meant that I could kind of understand in layman's terms. I don't mind; I just don't want too many people; if it was like a bunch of Consultants, then I wouldn't be happy, but one or two people'

A word query search was performed to find the 50 most frequently used words in the theme and these are displayed in the word cloud in figure 13.2. In word clouds, the larger the word in the figure the more prevalent it was in the analysis. The fact that the most common word is 'person' is not surprising. Many of the conversations detail individuals experiences and the groups reaction to them. Overriding discussions where related to the fact that each person is different and they each have their own barriers. The overlap with communication and personal feelings is also evident in the words.

Figure 13.2. Word cloud for most frequently used words associated with barriers to discussions

2. Communication factors

Communication skills was a theme that overlapped with many of the other themes. The establishment of solid patient –clinician relationships was a key feature that encouraged women to open up and feel comfortable discussing SF**.**

Methods of communication

When the participants were discussing communication, it was not just the verbal but also the non-verbal cues that the patients pick up on. It was suggested that the tone of the questions was important in helping the women feel at ease with discussions. The establishment of rapport within the consultation was a high priority for a lot of the women to feel that they could

truly open up about their issues and associated feelings. Women also wanted to be met with empathy and understanding and it was suggested that there were some clinicians who did not have the necessary skill to demonstrate that. Several of the women wanted the clinician to help rationalise the problems and help them to understand that it was not unique to them, and things could be done to help. However, it was recognised that some women will never be comfortable communicating about SF, whether it be with a clinician or partner. Several of the women reported having written down some of the concerns / problems before a consultation as they felt once in there, their own personal communication skills may be lacking and they didn't want things to be missed. Specific comments included:-

'Because it is such a highly personal thing and a lot of people would be very uncomfortable being asked it straight off. I think you have got to establish, for want of a better way of putting it, a relationship with your patient before you can broach something like that'

'Making them realise that it's not unique to them; they are not alone in that problem and I think that would make them feel more comfortable discussing it'

'As with any relationship, emotional, professional, whatever; it does come down to dynamics and maybe there are just some people who will never want to open up and you just have to factor that in and then there are others, who are probably not best professionals who aren't best placed to be asking those questions because they don't have the empathy or the understanding'

'It's all about your tone…how you ask the questions. That will straight away set me at ease or not'

'Some people just will never be comfortable discussing with someone they don't know, or even with their partners. It's the individual personality'

'I knew I wouldn't say half the things and once I start crying then I can't get it out anyway, so I wrote down everything I was feeling'

Personal feelings

The most emotive subtheme that emerged and overlapped with almost every other theme was around the participant's personal feelings. These were not only in relation to SF but also their Urogynaecological problems. Almost all of the women reported a degree of embarrassment or shame in relation to their problems. Although it was noted that discussing bladder problems has become less of a taboo in society many women still feel isolated and that they are alone.

'You have got the shame of having an overactive bladder and then talking about very personal issues'

'It's almost like you are ashamed'

'I feel ashamed'

'I'm so fed up of feeling that no-one feels what I'm feeling'

'I think also that now people talk about bladder problems, but when I first had it, there were no adverts on telly for pads and it really was taboo. I can remember when you would go and buy sanitary towels and they would put them in a brown bag so nobody would see them. Now it is much more talked about, but I still don't feel that it is something I want to go and shout about. I still feel that it is something personal to you'

For many of the women, when seeking help or having conversations about SF, the most important thing for them was to feel that they are being listened to by the clinician and to feel that the clinician cares about what they are saying. Many of the participants agreed the reaction of the clinician during a consultation was very important to their feelings and could positively or negatively impact on an interaction.

'As long as I can see that the person does actually care'

'I feel I want them to get into my soul and know what I need and that they understand what I'm feeling and advise me'

'I'm in tears, I just feel so awful that I just wanted the ground to swallow me up and this young doc, you can see he's dying'

What if we don't ask?

With so much of the focus of the discussions around discussing SF, one of the sub themes that emerged was related to how the participants would feel if they were not asked about SF or given the opportunity to discuss it, no matter how difficult those conversations may be. Almost all of the women agreed that they felt something would be missing in their holistic assessment if they were not asked and even acknowledged that they understood there may not be treatments available but they at least wanted to talk about it. Comments included:-

'As long as they do address it and I have the opportunity to voice my concerns'

"Do they think - well they're dead in the water, it doesn't matter"

'I would have been quite upset as it is almost negating part of me as a woman and I think we all have the ability to be SA and if it becomes an exercise in exclusion, that would make me feel really sad'

'Even if they can't do anything, talk to me about it'

Two word clouds were created for this theme, one looking at the most frequently used words associated with communication factors (Figure 13.3) and the other for personal feelings (Figure 13.4). The most prevalent words in the communication sub theme were person and comfortable. Again referring to the individual nature of how communication is perceived and how by being comfortable with the clinician, the surrounding environment and the topic eases communication. As previously noted these word clouds also demonstrate the overlap in the themes, highlighting the individual nature of the topic. The universal personal feeling was that of embarrassment, expressed by all participants in the FGs and used a total of 67 times in the conversations.

Figure 13.3 Word cloud of most frequently used words associated with communication factors

Figure 13.4 Word cloud of most frequently used words associated with personal feelings

3. Ways to introduce the discussion

This category links directly to one of the questions asked of the women in the FGs. There were many discussions based not only on how they had been approached about SF, but also how they would have liked the topic to have been broached with them. The discussions focused around three main areas, one on verbal questions related to how SF is introduced and how questions are asked, one detailing written methods of communication and the third theme that emerged from the data was regarding a desire for pre-warning. Most of the women agreed that one single method was not ideal and that using the written word as well as a conversation was the best approach.

<u>Written methods</u>

Two thirds of the women felt that the use of a questionnaire was a useful tool to either introduce or further probe the topic of SF. It was considered by the woman, that completing a questionnaire prior to a consultation may be taken as a form of consent to discuss the topic, or a way of gaining a further understanding of problems for the women who felt too uncomfortable discussing the topic directly. Almost all of the women felt that completing a questionnaire was less embarrassing than having to answer the same questions when asked directly. Comments included:-

'For those who still feel uncomfortable talking to another being, whether they are female or whatever, you could offer the option of the questionnaire

'I'll put my feelings down on paper, as I am too embarrassed to bring it up in the session, but if it is already on paper, then they can broach the subject for you and ask you more probing questions around it'

'It would make it a lot easier, so that you can tick boxes and that might be a way of lessening the embarrassment for some patients'

'I think questionnaires are a good way of maybe gaining consent'

'I would much prefer everything to be on my questionnaire; I can be as honest as I want to; skip what I want to; put in what I want to and it is all done on paper and I don't have to feel embarrassed or offended at my actual appointment'

However, many of the women did have concerns regarding the content of the questionnaire, feeling that issues surrounding SF do not always fit into a tick box in the same way as questions related to bladder function. Several of the older women were also concerned about the potentially explicit nature of the questionnaire, feeling that questions about certain sexual practices may make people uncomfortable and that they should be given the choice as to how and if they would like to further discuss the topic of SF. All of the women agreed that all questionnaires on SF should include a comments box, that would allow them to voice individual concerns that they had and felt that by putting it in writing for the HCP to read made it easier to talk about during the consultation. One simple option discussed was to just have a single question on paper asking the woman if she would like to discuss SF and then a space to note concerns to discuss. Comments and suggestions included:-

'They are structured such that I did not really know what to put down on the form and sometimes that tick box, with something that is personal like sex, doesn't always apply in the same way as; how many times do you pee a day'

'Obviously you would have to be very cautious because, probably, if you were to give "do you do this, this, this and this" some peoples eyeballs might fall out'

'Give them the option; there is a questionnaire we would like you to complete; however, it is extremely personal, some might say invasive, if you are comfortable with it, fine, but if not you don't have to complete it'

'I think a questionnaire would be good, possibly asking to tick the box if you would be happy to discuss those matters and I think that takes out the awkwardness for both parts really, when you actually get to the appointment'

'Also a comments box, because sometimes what I hate with hospital things, I think "well I'm A&B but I'm not that". So just to be able to put a comment, because once I know you have read that, it's easier for me to talk about it, rather than me to sit there and bring it up'

Conversation starters

Many of the women had ideas about how they would like to be asked regarding SF and suggested ways which the questions could be phrased to help minimise the impact. Many agreed that by ensuring that the woman understands why the clinician feels it is important to ask about SF, for example by linking it to common problems experienced by other women, it may normalise the issue, reduce embarrassment and help them to not feel alone. Suggestions included:-

'You can ask the question, "Are you sexually active" and if they say yes/no, you can tactfully ask "Is that through choice"; "would you like to be more sexually active, but you find that this problem prevents you, or is it because of other factors which are not relevant to why you are here"

'If you were to say "we find that a lot of our patients experience this", they might say, "oh yes, I had that"

'I think maybe, "A lot of our patients with similar problems to yours experience difficulties in their sex lives; do you have any issues; are you sexually active; if not, is that because of your issues". It's not so brutal. "A lot of our patients experience problems, would that apply to you?"

There were also questions about needing further clarity with terminology as it was felt that the term 'sexually active' could be misconstrued and that when asked about problems with SF it had quite negative connotations. It was considered that for women that are in long term relationships, they may not have had vaginal intercourse for a long time often due to partner health issues, however, they still found ways to be intimate and have a happy and fulfilling sexual relationship. It was felt that the terminology is too exclusive and directional and not representative of the population.

Many of the women in the group agreed that the important thing was about their enjoyment and that instead of asking if their UI/POP symptoms caused any problems with the sexual lives, that asking instead about the impact their UI/POP had on their sex lives was preferable. There was also agreement in the groups that at the start of the discussions the HCP should add a rider

that if at any point in the conversation the patient became uncomfortable they can stop. Quotes included:-

'What does sexually active mean?'

'I think it is wording things so that they are as inclusive as possible so as not to deny someone the opportunity'

'Are you sexually active is too directional'

'Enjoy is a good term and I quite like impact'

'If at any point you feel that you are uncomfortable during our chat, just stop; I won't be at all offended'

Pre-warning

This sub theme emerged and overlapped with all of the core categories identified. It was reported by the women in both FGs that when you attend a Urogynaecology clinic, it is not automatically considered by the patient that HCPs will be asking them about SF as they are concentrating on the presenting complaint. By having some idea before the clinic appointment about what to expect on the day and the sort of questions that may be asked women felt that this would help them to mentally prepare for the appointment and consider if they wish to broach the subject of SF and what concerns they have. This also overlapped with the idea of a questionnaire to complete beforehand as the women felt that it would help them to focus and verbalise their concerns. Comments included:-

'Putting it in the letter that goes out to the patient that this is what is going to take place, so that the patient is mentally prepared for the questions that they can ask, because sometimes you go into an appointment you are not aware of what you can or can't ask'

'You have got the time to think about it, rather than being under pressure and not remembering. If you have the questionnaire beforehand you can think about what are my issues'

'It comes to having something beforehand'

'I think having the opportunity to think about what is happening to me and being able to document that before I go to my appointment, it's very important. At the appointment, I've probably been having a busy day and I won't remember, or be embarrassed or whatever, but if it's all down on paper, then I know they have all the information and they can ask me questions from there'

The concept of pre-warning was also discussed in relation to several of the barriers identified by the women in previous conversations. It was felt that by knowing that these conversations were going to take place in a consultation, women may decide not to bring their partners with them to avoid the awkwardness of being asked with them present or request to see an alternative HCP (a female clinician) when they arrive to ensure that they saw someone they felt comfortable discussing identified issues with. Quotes included:-

'What you wouldn't want is to go in unaware and to be asked questions that actually you really want to talk about, but not with them'

'I think you need to ask the patient before they attend the appointment, because I know that if I came with my husband and you said that you wanted to ask some sensitive questions about my sex life and would I like him to stay or go; I would feel really uncomfortable asking him to leave the room, I know I would worry about how he felt about that. I think if possible, I would prefer to be asked before I arrived at the appointment; then at the appointment you could ask him to step outside for a while and it wouldn't look like you have had them banished from the room'

Discussions

The participants in each FG were quite similar and ensured that an appropriate range of parity / presenting conditions / social status was present. Although the majority of participants were in the normal age range for women visiting our clinics, it would have been better to have representation from the under twenties and over eighties to ensure the full range of opinions was sought. It is also noted that we did not have any women representing the LGBT community nor did we have any women in the post-partum period. This may potentially mean that data have been missed and that some of the themes generated may be incomplete and invalid. Although, in view of the aims and problems with the intended main trial, it may have been more appropriate to only include women with OAB / DO in the focus groups, in real life practice we do not separate these women from those presenting with other urogynaecological complaints so when trying to address our approach to sexual function we needed to include all women attending our clinics to ensure that any changes may also be generalisable and relevant to them as well.

It was apparent from the FGs that most women do appear more comfortable discussing SF with a woman. Hall et al (2002) performed a reciprocal likeability study and found that female clinicians like their patients more than male clinicians and that the patients liked their female clinicians more than the males. If a patient likes his/her HCP then this is going to help them feel more comfortable during personal discussions. Hojat (2007) reported that female clinicians score higher in empathy than their male counterparts and this was one of the important factors for women in the FGs. Interviews of women with OAB regarding HCP-patient communication also found that women preferred to talk to a female HCP as many reported that their male clinician ‘does not understand’, ‘is not concerned’ or ‘this is not important to him’ and this led to an overall dissatisfaction with the quality of communication regarding OAB (Filipetto et al (2014).

The HCPs did not consider that their age was an issue, however, for some of the women in the FGs if the HCP was considered to be too young, it would change their initial preference in sex of the clinician. According to Fiske et al (1999), people stereotype on two different dimensions, the first being friend / foe (warmth) and the second being capability (competence). While people stereotype their own preference as both warm and competent, they judge most outgroups ambivalently by ascribing both negative and positive characteristics to them. For the women in the FGs, this is what appears to have happened with sex and age of the clinician. Warm and competent is an older female clinician, warm but incompetent would be a young female clinician, cold but competent would be an old male clinician and the worst outcome of cold and incompetent is a young male clinician.

Issues with terminology related to SA has already been reported as a problem in the clinical trial reported in chapters 6-9 and within the prevalence study in Chapter 12. However, it was also a key point within the FG's with women feeling they needed more clarity on what is actually defined as SA and an overall feeling that the term SA is too directional and exclusive.

The sub theme that considered sexual inactivity as a barrier to discussing SF was quite surprising. I was unable to find any literature relating to the concern that women do not understand why they are NSA or regarding the development of new sexual relationships and the impact that LUTS may have on these. However, for a significant number of women in the groups this was an area of real concern and it could be hypothesised that initiation of new sexual relationships may also cause anxiety related to body image / desirability / performance and if there are additional concerns associated with LUTS for example fear of leakage / smelling during sex or the concerns over disposal of incontinence pads, these increased anxieties may further restrict or prevent women from engaging in new sexual relationships. Further research into this concept is necessary to fully understand the issue and how HCPs may help and guide women to overcome this barrier.

The sub theme ‘What if we don’t ask’ also seems contradictory. Women appear to report significant barriers to discussion, however, report that they would feel that their assessment was incomplete if they had not been questioned regarding SF and that it was considered a slant on their womanhood when not mentioned. This highlights the fact that although these discussions may be difficult for women, they are of significant importance and HCPs need to ensure that they work on breaking the barriers and taboos associated with SF, in order to provide optimal care and assessment of their patients.

The word ‘embarrassment’ was one of the most frequently used words within both the FGs. The concept of embarrassment in health care has been proven to deter patients from seeking help (McKie 1993), add to the discomfort of chronic problems such as UI (US DoH 1992), and deter staff from broaching the topic of sexual function (Kelleher & Oxenham 1993). However, it is not just the embarrassment of the patient that is a barrier but also that of the clinician. Meerabeau (1999) performed a review of the literature on embarrassment, in healthcare, particularly related to consultations / examinations regarding sexual issues. She summarised that ‘the current literature indicates that nurses and doctors have not shed the understandings acquired in their primary socialisation, which has taught us that sexuality is a private affair’. It could be considered that helping HCPs to overcome their embarrassment should be the first point of training, before trying to break down the patient barriers to facilitate effective communication on issues of SF.

Personal discomfort and embarrassment regarding SA has been established as a barrier to help seeking behaviour in women (Nicolosi et al 2006) and UUI is especially associated with feelings of embarrassment (Brown 1998, Van der Vaart et al 2002, Norton 2003). As many of the woman attending our service report symptoms of UUI, it raises the questions ‘do women with OAB have increased levels of embarrassment discussing SA compared to those with other LUTS? There were no studies identified in the literature to address this question.

One of the unexpected findings of the FGs was that some women felt that the subject of SF was best raised before they attended a secondary care service by their GP in primary care. It was considered that often patients have a long term relationship with their GP and due to this already established rapport, initiating the conversation at this stage may be easier. However, concerns over GP time restraints were the limiting factor why this was not taking place in practice.

Many of the women felt that a questionnaire, completed before their consultation would be preferable, to allow them to explore their own personal thoughts and reduce embarrassment associated with the conversations. This is acknowledged by Abrams et al (2017) who suggest that for patients who find the discussion of intimate issues with HCPs very difficult, questionnaires may allow these issues to be measured in private, at ease and more effectively before exploring the questionnaire responses in a clinical interview. The women did not discuss how they would like to complete these questionnaires ie on paper, or online via a computer at home or a tablet in the outpatients setting. It could be considered that women find answering questions on a computer easier than talking to someone, but it could also be considered impersonal and for women who are not computer literate a barrier. Again, a questionnaire is not suitable for all as there will be women in the clinical population who are illiterate or in our diverse population, unable to read and write in English.

One of the key points from the FGs was in relation to the desire for pre-warning regarding the types of discussions that may take place during a consultation. The concept of pre-warning about the context of consultations and the likelihood that intimate questions may be asked is not new. Tomlinson & Milgrom (1999) reported that some doctors get over their initial embarrassment and the shame / humiliation of the patient by giving them a pre-consultation questionnaire that introduces the discussion and identifies concerns. This is similar to what the women in the FGs were discussing, however, many patients in the study disliked its anonymity and apparent

coldness. This would need to be considered if some form of pre-warning was to be developed. Although there are now 17 questionnaires to assess sexual function / sexual health and urinary symptoms in women, with a Grade A, B or C rating (Abrams et al 2017) none of these contain questions relating to whether women wish to further discuss their concerns or answers on the questionnaire with their HCP. The pre-warning concept also relates to their decision regarding who they bring into the consultation room with them yet, our current practice does not advise them of possibility of intimate discussions taking place during their appointments or ask any form of questions prior to their visit.

Limitations

When distributing invitation letters, stamped addressed envelopes for the service were not provided. This could potentially mean that for women who do not have access to email or telephone (for example to due educational / social or financial reasons) they were unable to contact us to take part and may have had a different opinion that we have missed. It is also recognised that this is a self-selecting group of women and this in itself may cause an inherent bias in the findings of the group. It could be suggested that the women who do not come forward to discuss approaches to SF in a FG are also the women who struggle in clinical practice and are therefore a cohort that we need to understand further and who have been missed in this study. I also did not note the marital status of the women to ensure that there was a range of single, married, divorced and widowed participants as this may have impacted upon their opinions.

Although one to one interviews may have been more appropriate to probe individual experience, as I wanted to generate ideas for service improvement and development, focus groups were chosen as the method of data collection.

Another limitation of this study is in the reliability of thematic analysis and reliability of perceptions as these may not always be accurate and my own

opinions and beliefs could have affected the way it was performed. Some of the sub themes may have be introduced by the researcher within the FG's however, the aim of the FG's was to explore the barriers etc and what emerges is what comes from the patients. We were able to categorise the themes from the subthemes. The fact that the second data analyser was not a specialist in the field of urogynaecology and through member checking it is hoped that personal perception as not influenced the data. It is also important to remember that the data obtained from these FGs and subsequent analyses are very context specific and not generalisable to other institutions.

Quality of the analysis

All of the discussions in the FGs were digitally recorded and transcribed however, they are missing the murmurs / nods or ascents of agreement with statements that women may have displayed during the discussions. These were recorded in the scribe's notes and my memos which were written directly after the FGs and were included in the analysis. However, there is the risk of a bias from my recollection. Although the use of data tracking and audit trails used during this analysis (which is a key feature of GT methodology) should have countered this risk of bias.

Directly after each FG the scribes notes and memos were analysed and the transcripts were typed within two days of the focus groups so that analysis could take place as quickly as possible and the initial analysis of the first FG was performed before the second took place.

In order to ensure reliability and objectivity in the analysis, the second independent researcher was given the list of codes and asked to identify sentences related to each code. Over 80% of the sentences matched the original reviews and those that did not match were assigned to overlapping themes suggesting good reliability.

There were no changes of opinions of participants in the FGs suggesting that there were no dominant voices that the women felt pressured to conform with, or change their perception/ beliefs to align with their suggestions and this is also a sign of good reliability.

Levels of agreement were based on the transcripts, scribe notes and memos. The women in the groups only completely agreed on three minor details:- that SF should not be the first question asked in a consultation, that any questionnaire developed should have a free text comments box and that clinicians should reassure women that conversations regarding SF can be stopped at any time if felt to be too distressing or personal. Although for several of the other salient points there was agreement with the majority of women. Although this point could be considered as a sign of poor reliability, it was felt that this just highlighted the individual nature of the discussions and the realisation that no one size will fit all in approaches to SF.

Therefore, a woman centred, individualised approach is justified, but for many a combination of a pre-consultation questionnaire alongside direct questioning during the clinical consultation appeared to be the preference.

My reflections

It is the responsibility of the GT researcher to capture the reality of the data and to not allow his / her own assumptions to impact upon the analysis. However, in reality this is very difficult to do as when you are so involved in the topic and have spent a lot of time reading relevant literature, it can be difficult to stay impartial. This is true not only in my role of data analyser but also as a moderator. Again, this highlights the need for a method of audit and data tracking which is integral to GT.

In my role as a moderator, I believe that I allowed an open dialogue and demonstrated good interpersonal skills adapting to the flow of the discussions and allowing each participant to voice her personal views and comments in a non-judgemental way. I believe it was these communication

skills and the occasional humour in the conversations that influenced the participants to open up and be truthful.

I tried to avoid giving my own personal opinion during the FGs to avoid influencing the discussions but on occasion I did pass comment on current practice in KCH / other departments or views previously expressed by other women.

I think that I had the right level of involvement in FG1 and the conversation between the participants flowed very easily. I personally found FG2 harder to moderate and the women at times needed more encouragement to talk and additional questions to further probe their views and opinions were necessary to get the women to elaborate. I found this challenging as I wanted to probe opinions without trying to add an alternative viewpoint and influence the discussion.

When analysing the data and reviewing the core categories and sub themes, I frequently went back to the questions that I asked to assess if this influenced the discussions. The main point where I may have influenced the discussion was where I introduced the idea of a questionnaire on SF. Although I may have introduced the concept, the FG participants were completely responsible for the further suggestions regarding when it should be administered, what it should include and how it should be used to complement clinical practice.

One of the most satisfying aspects of running these FGs was the comments from the participants after the sessions and again when they have been seen in clinics since. Many of the women reported that they really enjoyed the session and that actually discussing problems with LUTS / SF with other people in a similar situation was really refreshing and helped them to realise that they were not alone.

I personally also enjoyed the FGs as it was really nice to have an informal conversation with our patients with the aim of improving our service. What I

would really like to do at a later date is to re-run the FGs with the same participants and refine and enrich the categories identified to further make sense of and develop the categories.

Clinical implications

There were many ideas that emerged from the data that could help shape and refine our current clinical practice. The first is in relation to the wording of the outpatient appointment letter. I will review the current template and add in an explanatory sentence that questions of an intimate / personal nature may be asked during the consultation. This will allow the patients to decide if they wish to bring a partner / friend into the consultation, or allow them to express a preference for the clinician that they see.

When searching the literature regarding pre-warning, two screening questionnaires for SF were discovered. The first is the Brief Sexual Symptom Checklist for Women (BSSC-W). This is a four item questionnaire that assesses if a woman is SA, if they experience any problems with SA and if they would like to discuss this with a clinician. It was developed by the International Consultation in Sexual Medicine (ICSM) (Hatzichristou et al 2004). The questionnaire is demonstrated in Figure 13.5. The second is the Sexual Complaints Screener for Women (SCS-W) which was developed by the Standards committee of the International Society for Sexual Medicine and consists of a series of questions concerning sexual experiences during the last 6 months (See Figure 13.6) (Porst 2009). However, there are no validation studies available for these tools (Hatzichristou et al 2010) and there are no acknowledgements of urinary symptoms. Potentially, a pilot study to assess the use of and validate a simple screening tool in practice based on these developed in the field of sexual medicine may prove beneficial to our patients.

Brief Sexual Symptom Checklist for Women (BSSC-W)

Please answer the following questions about your overall sexual function

1.Are you satisfied with your sexual function?

□ Yes □ No

If No, please continue.

2 How long have you been dissatisfied with your sexual function?

3a. The problem(s) with your sexual function is: (mark one or more)

1 Problem with little or no interest in sex

2 Problem with decreased genital sensation (feeling)

3 Problem with decreased vaginal lubrication (dryness)

4 Problem reaching orgasm

5 Problem with pain during sex

6 Other:

3b. Which problem is most bothersome (circle) 1 2 3 4 5 6

4 **Would you like to talk about it with your doctor?**

□ Yes □ No

Figure 13.5 The Brief Sexual Symptoms Checklist for women

Figure 13.6 Sexual Complaints Screener for Women (SCS-W)

This screener is a series of questions concerning your sexual experiences during the last 6 months. Each question can be answered by circling the condition that best characterizes your personal experience. ***Sexual activity*** includes any activity aimed at experiencing sexual satisfaction and enjoyment. The term sexual activity does not necessarily include sexual intercourse (vaginal or anal penetration)

1a) Some women experience lack of or low sexual interest/desire in sex. Has this happened to you during the last 6 months? Never/almost never Rarely Sometimes Often Almost all the time/Almost always

1b) Has this been a personal problem for you?
Not at all A very small problem Some problem A considerable problem A very great problem

2a) Some women do not experience physical sexual excitement (e.g., genital swelling, vaginal wetness, tingling sensation) during sexual stimulation and/or sexual activity. Has this happened to you during the last 6 months? No sexual activity Never/almost never Rarely Sometimes Often Almost all the time

2b) Has this been a personal problem for you?
Not at all A very small problem Some problem A considerable problem A very great problem

3a) Some women do not feel sexually turned on or do not have pleasurable sexual feelings when engaging in sexual activity. Has this happened to you during the last 6 months?
No sexual activity Never/almost never Rarely Sometimes Often Almost all the time

3b) Has this been a personal problem for you?
Not at all A very small problem Some problem A considerable problem A very great problem

4a) Some women experience difficulties reaching orgasm during sexual activities despite feeling sexually excited.
Has this happened to you during the last 6 months? No sexual activity Never/almost never Rarely Sometimes Often Almost all the ti

4b) Has this been a personal problem for you?
Not at all A very small problem Some problem A considerable problem A very great problem

5a) Some women experience genital pain during or shortly after sexual activity. Has this happened to you during the last 6 months? No sexual activity Never/almost never Rarely Sometimes Often Almost all the time

5b) Has this been a personal problem for you?
Not at all A very small problem Some problem A considerable problem A very great problem

6a) Some women experience difficulties allowing vaginal penetration despite their wish to do so.
Has this happened to you during the last 6 months?
No sexual activity Never/almost never Rarely Sometimes Often Almost all the time

6b) Has this been a personal problem for you? Not at all very small problem Some problem considerable problem great problem

7a) Some women experience persistent and unwanted genital arousal (tingling, throbbing, pulsating) in the absence of any sexual interest. Has this happened to you during the last 6 months?
No sexual activity Never/almost never Rarely Sometimes Often Almost all the time

7b) Has this been a personal problem for you?
Not at all A very small problem Some problem A considerable problem A very great problem

8a) During the last 6 months, my sexual life has been:
Very unsatisfying Unsatisfying Rather unsatisfying Rather satisfying Satisfying Very satisfying

10) Is there anything else you would like to tell us with respect to your sexual life? For those who have not been sexually active during last 6 months please explain why you have been sexually inactive.

11) Would you want your physician (counsellor) to further explore sexual difficulties and/or problems with you? No Not now Yes

Another area for change in clinical practice that can easily be implemented is to provide some training and education for all members of the MDT. This will include ways in which to normalise the discussion about SF and appropriate language to use including how to individualise assessment and adapt their style of questioning. Suggestions will also include the use of diagrams to help explain conditions / problems to women and at what point in a clinical consultation these discussions are appropriate. This training can also highlight the point that SA is a continuum and just because a women may not be SA at one point of asking, does not mean that that is always going to be true and that regular reassessment in required. It is already routine practice to reassess SF in women post-surgery for UI / POP or post-partum, therefore this needs to extend to all women who are NSA attending our clinics and not just specific patient populations. By engaging women in these discussions in a clinical setting, it may encourage women to discuss the topic of SF with their partners, family and friends which will help to normalise discussions and continue to break down taboos surrounding the topic.

Conclusions

Overall these FG have provided us with rich and valuable data regarding how we are approaching the topic of SF with women attending our service. The key points gained from the groups related to terminology and the desire for pre-warning regarding these discussions. There is the potential that because of inadequacies considered by some women in our approach, this may have negatively affected recruitment to the main study previously discussed. These new insights can help to develop our clinical practice and potentially help guide recruitment in future studies assessing SF in women with LUTS.

Chapter 14

Conclusions and Ideas for Future Research

Introduction

This final chapter aims to provide an overview of this thesis, highlighting the findings from these investigations and discussing the methodological limitations. Following this, recommendations for future research to further enhance knowledge in this field have been reported.

Overview of thesis results

The purpose of this thesis was to answer the question:-

'Does fesoterodine have any effect on the sexual function (SF) of women with OAB?'

This question was developed alongside the literature review reported in Chapters 2-5. Chapters 6 and 7 detailed the decision making and the methodology selected to answer this question which was an open label cohort study. Despite difficulties with recruitment (N=28 were recruited from a target of 132), the analysis reported in chapters 8 and 9, demonstrated statistically significant differences in both the primary outcomes (Change in item scores of the PISQ-12 and the SQOL-F at week 12 relative to baseline) and many of the secondary outcomes. The findings demonstrated an improvement in SF following treatment with fesoterodine in women with OAB. Although significant differences were found, the study design limits the inferences that can be made from this data. Without a randomised comparison group it is not possible to determine causality. Despite this, the study did confirm findings from other studies that in the clinical population studied, fesoterodine was a well tolerated, treatment for OAB symptoms which may also improve SF. Given the limitations of the study design it could be argued that a larger study – as was originally intended - would add little of value to these findings.

The analysis of the patient goals from the SAGA questionnaire, described in Chapter 10, provided new insights into the impact of OAB on women's

quality of life both physically and psychologically. The themes of 'finishing the task in hand' and 'being free to' highlighted that for many women it is not the symptoms of OAB that cause the greatest distress but the role and life limitations as a result of the symptoms. This raises questions regarding the validity of current QoL questionnaires as they may be missing important factors that could help clinicians to tailor advice and treatment for example how to manage taking the dog for a walk or sitting through a film at the cinema without needing the toilet. The lack of SF goals in the SAFINA study raises questions about whether SF is important to patients although it may also indicate a reluctance to identify improved SF as a goal.

Two key problems emerged from the clinical trial. Firstly, a number of centers did not always ask about sexual activity (SA) or reported challenges asking about SA despite this being part of the protocol and a fundamental aspect of the study. Secondly, the lack of a standardised definition of SA and a standardised time frame for assessment of SA has led to assumptions being made about what SA constitutes and this is a substantial impediment to research in this field. This meant that the populations in this trial (Chapters 6-9) was never accurately described and was likely to be one of the reasons for the poor recruitment.

Following the discussions in Chapter 9 regarding methodological limitations, it was acknowledged that presumptions had been made in the trial regarding women being SA and being open to discussing SA and SF. To understand how these presumptions may have had a negative effect on recruitment, two further research questions were raised:-

1. What is the prevalence of SA in women with OAB attending a London Urogynaecology outpatient service?
2. How do women want to be approached about the topic of SF?

Chapter 11 described the methodology employed to answer these two new research questions.

The SA prevalence study reported in Chapter 12, was designed to assess the prevalence of SA in our OAB population, to evaluate why women were NSA and to investigate variations between the SA and NSA groups. It revealed that fewer women were SA than expected and for the majority of those that were NSA it was due to the lack of a partner rather than due to their bladder / bowel symptoms or other health conditions. The psychological components of fear and anxiety related to UI and SF was very evident and raised several areas for further research suggested later in this chapter. However, analysis also revealed problems with the validity of the questionnaire in particular with non-response to questions as many women struggled to identify themselves or fit their answers / views into the preset responses.

The purpose of chapter 13 was to explore how women wished to be approached to discuss SA and SF in clinics. Focus groups were undertaken to elicit women's thoughts and views on this. The concept of 'pre-warning' regarding the topic of SA and SF and the potential use of screening questionnaires were themes that emerged and provided ideas for changes in practice that may be implemented in clinical services and research to enhance the ways in which we communicate with women about SF. These findings also emphasized the point that no single approach will work for everyone and as with all clinical encounters, care and communication should be individualised for each patient. It also highlighted the point that often a holistic approach to SF is overlooked with the focus of consultations geared towards specific symptoms during sex, for example pain and UI. Yet, the focus groups revealed that sexual health (including desire, sexual satisfaction, relationship satisfaction) is as important to women, if not more so than individual symptoms.

At the start of the thesis, a presumption was made the SA was a term that was well understood by women. There had been no indication from the literature review regarding the absence of a definition or the need for one and the term 'sexually active' had therefore been assumed to be good enough. This means that when women were asked the question 'are you

sexually active?' that there would be a common understanding of this term. But, as demonstrated during the focus groups and the prevalence study, there are many different ideas about what SA is and what it may involve. Potentially, given all the variations in what SA may include, this may mean that we missed women who would have been eligible for recruitment into the study or conversely that we actually recruited women who were not suitable and this may affected the reliability of the data. This also has wider implications for all clinical research into the field and for how women are being advised and counselled regarding SA.

Summary of Limitations

The most significant methodological flaw in the study was the lack of a comparator or placebo arm. As discussed in chapter 6, there were several reasons for this including lack of funds, provision of a placebo and timescales. Future studies could potentially use a cross-over design with an extended wash out period at the start of the trial, as this could be considered to be a placebo period and used as a comparator, but this may negatively impact recruitment as it delays treatment.

The lack of valid and reliable research tools has been highlighted as an issue throughout this thesis. This is not only because of the concerns already raised over the definition of SA or lack of. The only tool designed to assess women who are currently NSA (PISQ-IR) does not seem to be fit for purpose as discussed in chapter 12. Given the subjective nature of SA demonstrated in the focus groups the ideal research tool will have to include some open ended questions to encompass all views as many women do not feel that they fit into a typical 'tick box' classification.

Throughout this thesis there have been many discussions regarding the barriers to recruitment and one of the fundamental issues was related to how the clinicians approached women regarding SA and how they took a sexual history. With multiple research sites and trial personnel, there may have been a significant variation in the way in which women were approached,

and the depth of discussion on sexual function. The focus groups confirmed that many women consider our current approach inadequate and have provided ways in which our approach can be modified and developed. For future studies, the findings from these focus groups would be used to develop a recommendation of how to approach women and take a sexual history and to ensure all study staff are educated appropriately to use this in practice. This may reduce variations in the discussions regarding SF and foster more open discussions with women and potentially enhance recruitment.

Reflections on the thesis

When I started this project, I naively presumed that because the department had significant experience with OAB clinical research, that the traditional methods for recruitment employed in many other studies would work, regardless of the fact that this was the first study in the department looking at SF as a primary outcome.

The main problem with my approach to this thesis was that my background clinical knowledge was focused on OAB and I had not considered the complexity regarding the definition of SA. In line with this, I developed an OAB study but just changed the primary outcome to one focusing on SF. However, as my knowledge on SF and FSD has increased during the course of this work, there are many aspects of the trial protocol that I have recognised are not ideal in the assessment of SF (these are discussed in the next section).

During the course of this thesis I had the opportunity to spend two days with Dr Irwin Goldstein (Current President of the Institute for Sexual Medicine and International Society for the Study of Women's Sexual Health, Board member of the International Society of Sexual Medicine and founding editor of the Journal of Sexual Medicine) and Sue Goldstein (Sexuality Educator and Clinical Research Manager at San Diego Sexual Medicine Centre). I had the opportunity to discuss recruitment issues with them as I has been

unable to find any literature related to failed recruitment in SF studies. They reported that they had not had significant issues recruiting into clinical trials investigating SF. However, the big difference with their population was that all the patients had presented with sexual problems and made the first step of seeking help as the problem had become distressing and bothersome. However, in our cohort of women, they had sought help for LUTS and not sexual problems and unless the sexual problems was causing them significant distress then they were unlikely to agree to take part in a study that they feel was not relevant to them. It could be considered that we did not make it clear enough to women that we were not seeking those who reported issues with SF, but was assessing the impact of treatment on SF overall so that we could counsel women appropriately as to what to expect from treatment of their LUTS. In future work, clarity on the patient information leaflets may help to address this.

Ultimately, this process has demonstrated that knowledge in one aspect of research does not automatically mean that it is generalisable to other areas and that the initial stages of project development, including planning the methodology, reviewing the sample population and performing a pilot study are essential factors in successful research outcomes.

Discoveries that have emerged during the time frame that this thesis was undertaken and how they would influence future work

During the course of this thesis a number of articles / recommendations have been published in relation to developing / undertaking research in SF. Based on this new information, there are several aspects of the study methodology that would need to be altered for future research.

The trial only assessed change in SF over a 12 week period and it could be considered that this was too short term to show any long term benefit in an outcome which may occur infrequently. It has since been recommended that all clinical studies in FSD are at least 24 weeks (Fisher et al 2017). This longer time scale may allow for more meaningful data to be collected.

Although the CTIMP did follow up the participants at the 24 week stage, this was only to assess persistence with medication and adverse events but it should have included a further assessment of SF.

The exclusion criteria were also restrictive and aimed to fit the women into a 'pure' OAB / DO group. In real world clinical practice, there are many women with OAB symptoms for example those with de-novo OAB following continence surgery or due to neurological problems that were excluded from this study and it could be considered that the number of 'pure' OAB patients in practice is low therefore our timescales / recruitment numbers were unfeasible from the outset. If the inclusion / exclusion criteria were less stringent it may have helped to improve recruitment and although this could also be seen as a limitation to the research as the group would be less homogenous it would mirror the actual cohort of women that are attending our clinics and potentially be more clinically meaningful for practice.

The choice of questionnaires used as outcome methods could also be criticised. According to the recommendations by the International Consultation on Sexual Medicine, research into SF should include a validated self-reported measurement of SF which includes domains and subscales related to the phase of the sexual response cycle and /or DSM-5 diagnostic categories and or questionnaires or structured interviews assessing SF foci and able to measure change over time with an intervention. A validated measurement of sexual distress is also essential as evidence of distress is required to diagnosis FSD (Fisher et al 2016). There was no measure of sexual distress used in the original CTIMP and this would need to be included in any future research. The PROMS used as the primary outcome in the study, although validated may not have been the ideal ones to use as according to the International Consensus on Sexual Medicine the FSFI should now be the questionnaire of choice in all SF studies (Fisher 2017).

In 2013, the DMS-V (APA) revised the terminology related to SF and FSD (as discussed in Chapter 2). Given the changes in terminology during the

course of this thesis, the biggest challenge has been deciding how to describe or refer to the outcomes now. Ultimately, if the DSM-5 guidelines are strictly followed then none of the women who participated in this trial could be classed as having FSD due to their underlying LUTS and the fact that we did not assess the frequency and length of time with these symptoms and the distress that they cause. For any future work, although we can assess SF and distress in these women, it is unclear how they should be labeled if they have poor SF and report significant distress associated with this as they do not fit the FSD definition due to their LUTS.

Another area that was not previously considered was the potential for participation in the trial to act as some form of sex retraining / therapy for women. In the same way that discussing issues, attending appointments where written and visual information is readily available and completing questionnaires can act as a form of bladder retraining and has been shown to contribute to the placebo effect in OAB trials, it is unknown if just opening up about issues and participating in the trial has the same effect on SF outcomes. It would be interesting to further investigate this area and a review of the placebo effect in other sexual function trials would be a starting point to explore this.

What have I personally learned from the investigation?

Over the course of the last eight years, I have gained a varied knowledge not only in the topics of OAB and SF but also the wider field of urogynaecology, urology and sexual medicine as I have been reviewing the surrounding literature. I have also gained a significant knowledge with regards to pharmacotherapy and have qualified as an Independent Nurse Prescriber.

I have always been determined and a hard worker, particularly with regards to further education. Yet, with all the challenges and difficulties along the way, not only with getting the CTIMP up and running but with the recruitment difficulties and additional investigations, has shown a resilience that I did not know I possessed.

I think that the most significant lesson that I have learnt during the course of this thesis is ‘Don’t ever presume’. This is not just true for the research methodology and trial processes but also the clinical population, terminology and individual patient responses.

Has it changed anything for my patients?

I believe that one of the most significant differences that this project has made to my clinical practice is in the way that I communicate with women about SF. I feel far more comfortable initiating discussions, understanding issues and knowing how to assess women with sexual problems. My increased knowledge and experience from the research has enabled me to share these learnings with patients, which can help to normalise the discussion, encouraging them to open up and potentially seek solutions and management strategies.

I feel that this increased knowledge and confidence has also changed how I counsel women with regards to therapy, particularly by trying to understand their individual treatment goals and tailoring care to meet their needs.

The work from the FGs has provided several areas for service development, especially simple ideas such as changing the information in our outpatients appointment letter to include a ‘warning’ that discussions regarding SF may take place during the consultation. It is hoped that these changes may help to improve the overall experience of the women attending our service and improve discussions on SF.

Follow up actions

There are several follow up actions that I have for the Urogynaecology department at KCH based on the feedback gained from the focus groups in Chapter 13. These include:-

- Change to the appointment letters sent to women to include a statement that discussions of a sexual nature may take place. This will provide a pre-warning to allow the women to consider their thoughts and decide who will attend the appointment with them.

- Validation of a screening checklist such as the Brief Sexual Symptom Checklist for women. This short questionnaire could be given out to women when they check in for their appointments or sent out with their appointments. It will not only provide pre-warning but will help identify women who wish to engage in further discussions regarding SF. However, there are no validation studies for this tool so these would be needed to consider its use in routine care.

Recommendations for future research

There are several areas of development and investigation that are recommended by this thesis to support future work in this field. These include:-

- Development of a standardised definition of sexual activity (including time frames)
- Development of standardised terminology for sexual dysfunction in women with LUTS
- Development of a valid and reliable research tool to assess women who are not currently SA and the potential impact of LUTS on their sexual status

- Development of a recommendation for HCP's regarding how to approach women regarding SA and take a sexual history to standardise and aid recruitment for future studies
- Investigation (and quantification) of the 'placebo effect' in clinical trials addressing SF
- Investigation of how many women re-engage with SA following treatment for OAB
- Review of QoL questionnaires to improve relevance to women's daily life

During the course of the literature review, analysis and discussions, several other areas for further research have also been identified. These include:-

- A systematic review of qualitative studies questioning if anticholinergics improve SF in women with OAB.

- Does a partner's SF improve if a woman's UI / OAB is treated?

- Investigation on the impact of OAB on the desire to start / the process of starting a new relationship

- Anxiety has been noted throughout this thesis to have a significant impact on women in relation to their OAB and SF yet there are still many areas / questions that remain unanswered. Just a few of those ideas include:-

    - Assessment of baseline anxiety scores - are their differences between those with OAB wet and dry?
    - Which came first the LUTS or anxiety
    - Assessment of anxiety scores pre and post treatment for OAB
    - Investigation of anxiety related to SF
    - Relevance of emotional factors in the development and maintenance of OAB / UUI and how this may affect treatment outcomes

Conclusions

The conclusions of this thesis are that there are indications that fesoterodine may have a positive effect on women's sexual function. However, it is not certain due to the lack of a comparator group. The thesis also showed that the current tools to assess SA are limited and that the prevalence of SA in our population is lower to be expected. Our current approach to discussing SA and SF with women is deficient and methods were identified that may potentially improve how women are approached regarding SA.

Overall, this thesis has highlighted the inadequacies in current research related to SA and SF and OAB and has made recommendations to develop definitions and research methodology to enable future studies in the area.

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INVESTIGATOR-INITIATED RESEARCH (IIR) GRANT APPLICATION

Instructions

This grant application form has been designed to facilitate the submission and review of requests for support of investigator-initiated research. This form has been designed to be completed in a word processing application. Fields will expand as necessary.

Concept

Pfizer will accept study ideas and outlines of concepts for preliminary review. If submitting concept proposal, the following minimal information on the form highlighted with an asterisk (*) is required:

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Please complete all fields that apply to the type of research you plan to conduct, and supply the following required documentation. Indicate N/A in those fields that are not applicable

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PRINCIPAL INVESTIGATOR CV (or complete the attached one page CV)

Your signed request letter, on official letterhead, should include the following:

- Title of study
- Brief explanation of research or rationale
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- Whether Pfizer drug is requested (specify estimated quantity)

INVESTIGATOR-INITIATED RESEARCH (IIR) GRANT APPLICATION	
INVESTIGATOR INSTRUCTIONS*: Please complete all fields relevant to your research.*	
PRODUCT(s) NAME *	Toviaz® – (fesoterodine fumarate)
PRINCIPAL INVESTIGATOR NAME *	Professor Linda Cardozo
ADDRESS * *(Principal Investigator's Mailing address)*	Urogynaecology Department, Suite 8, 3rd floor, Golden Jubilee Wing, King's College Hospital, Denmark Hill, London. SE5 9RS
TELEPHONE, FAX AND E-MAIL *	Tel 0203 299 3568 fax 0203 299 3449 linda.cardozo@compuserve.com
INSTITUTION and DEPARTMENT *	King's College Hospital, Urogynaecology Department
SITE COORDINATOR and CONTACT INFO. *(Name, telephone, fax & email)*	Angie Rantell Tel 0203 299 3568 Fax 0203 299 3449 angela.rantell@kch.nhs.uk
STUDY PROPOSAL DETAILS	
PROPOSAL TITLE *	A 12 week, single centre, open label study to evaluate the effect of fesoterodine flexible dosing regimen on the sexual function of women with overactive bladder.
RATIONALE * *(Provide a brief summary of the rationale for the concept/proposal and provide supporting references or unpublished data, if appropriate. The hypothesis or clinical question to be considered should be concisely stated and the trial design chosen should be appropriate to test the hypothesis.)*	The Overactive bladder Syndrome (OAB) is the term used to describe the symptom complex of urinary urgency with or without urge incontinence, usually with frequency and nocturia[1]. It is reported that the prevalence of OAB in the general population is 14-16%[2]. OAB is a distressing problem that can seriously affect an individual's quality of life by forcing them to alter their social, physical, occupational and sexual activities. Anticholinergic drugs (also known as antimuscarinics) are the mainstay of treatment for OAB symptoms. In the UK in 2007, 2.85 million prescriptions were written for anticholinergic drugs[3]. Fesoterodine fumarate is a new addition to this class of drug and is available as sustained release tablets in flexible dosing (4mg and 8mg). Several reports have shown the negative impact of OAB on sexual health, but there are very few studies looking at the impact of anticholinergics on the sexual function of women with OAB. Hajebrahimi et al[4] evaluated the impact of tolterodine IR on sexual function in patients with OAB and they concluded that tolterodine IR significantly improves sexual function of women with OAB. We plan to investigate the effect of fesoterodine on the sexual function of women with OAB as there are currently no studies looking at this.

RATIONALE * *(Provide a brief summary of the rationale for the concept/proposal and provide supporting references or unpublished data, if appropriate. The hypothesis or clinical question to be considered should be concisely stated and the trial design chosen should be appropriate to test the hypothesis.)*	**Null Hypothesis** Fesoterodine has no effect on sexual function in women complaining of overactive bladder syndrome. **Primary Objective** The primary objective is to assess the impact on sexual function, of 12 weeks flexible dose fesoterodine in women with OAB compared to baseline. **Secondary Objectives** • To assess the use of flexible dosing of fesoterodine on micturition frequency per 24 hours, nocturnal micturitions per 24 hours, urinary urgency incontinence episodes per 24 hours and urgency episodes per 24 hours after 12 weeks compared to baseline. • To assess the effect of flexible dose fesoterodine on treatment satisfaction and health related quality of life measure at 12 weeks compared to baseline. • To assess the tolerability of flexible dose fesoterodine in women with OAB. • To assess the impact of fesoterodine on bowel function. A full protocol detailing secondary endpoints, assessment, inclusion / exclusion criteria has been provided with this form 1. Abrams P, Cardozo L, Fall M et al, 2002,,Neurourology and Urodynamics 21 (2), 167-178. 2. Irwin D, Milsom I, Hunskaar S, 2006, Results of the EPIC study. European Urology, 50, 1306-1314. 3. Roesner M, Wagg A, 2008, , Guidelines in Practice, 11,7,27-32. 4. Hajebrahimi S, Azaripour A, Sadeghi-Bazargani H. J Sex Med. 2008 Dec;5(12):2880-5
STUDY PHASE (e.g. Phase I, II, III, IV)	Phase IV
ESTIMATED STUDY TIMEFRAME *(From study initiation to completion of analysis)*	2 years

***Minimum requirements for the submission of a concept.**

INVESTIGATOR-INITIATED RESEARCH (IIR) GRANT APPLICATION

STUDY DESIGN ***(Please Check One)***

X **SINGLE CENTER STUDY** **COOPERATIVE GROUP** **MULTI-CENTER STUDY**

***If multi-center study, list number of sites*:_____**

*If **multi-center** and Pfizer is to supply drug, please indicate if it is acceptable for drug to be shipped to primary site ONLY*

YES **NO** ***If no, list number of shipment sites:***

NO. OF SUBJECTS (target enrollment)	Based on power calculation 130 subjects need ☐ ☐
DOSING REGIMEN *Provide a schema or summary including all treatment modalities, and the dose/schedule/route of all agents, amount of drug requested. For Phase I studies, state the starting dose(s) and the dose-escalation scheme to be studied, and estimate of amount of drug requested.*	All participants started on Fesoterodine 4mg for 4 weeks. Then participants given the option to dose escalate to 8mg or remain on 4mg for the final 8weeks of the study. ☐

SUPPORT TYPE

What support is requested from Pfizer?

Drug X Yes No

If yes, X Finished Goods Pure Substance Can site

receive drug in bulk and repackage? Yes X No

Specify amount of drug being requested ☐ ☐ ☐ ☐

As this study allows each participant to decide if they wish to dose escalate an estimation of drug quantity can only be expressed as a minimum and maximum doses required. ☐ ☐

Fesoterodine 4mg minimum of 4550 doses,

maximum of 12740 doses Fesoterodine 8mg

maximum of 8190 doses

Pharmacy contact name, phone number and shipment address (receipt of study drug):

Joanne Gordon, Senior Clinical Trials Technician, Pharmacy Department, King's College hospital, Denmark hill, London, SE5 9RS, 0203 299 3506

Are you requesting funding	X	Yes	No

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The synthesis of art and science is lived by the nurse in the nursing act

Josephine G Paterson

Assessment and diagnosis of overactive bladder in women

Rantell A (2013) Assessment and diagnosis of overactive bladder in women. Nursing Standard. 27, 52, 35-40. Date of submission: December 3 2012; date of acceptance: May 25 2013.

Abstract

Overactive bladder (OAB) is a distressing problem that affects many women in the UK. Symptoms of OAB include urinary urgency with or without urgency incontinence, usually with frequency and nocturia. This article discusses the assessment of women reporting lower urinary tract symptoms, including simple tests to be performed and specialist investigations that may be required before a diagnosis of OAB can be confirmed.

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Keywords

Assessment and diagnosis, lower urinary tract symptoms, nocturia, overactive bladder, urgency incontinence, urinary incontinence, women's health

Review

All articles are subject to external double-blind peer review and checked for plagiarism using automated software.

Online

Guidelines on writing for publication are available at www.nursing-standard.co.uk. For related articles visit the archive and search using the keywords above.

PATIENTS WITH SYMPTOMS of urinary urgency or incontinence usually present to and are identified in the primary care setting (Department of Health (DH) 2000). Assessment and diagnosis of overactive bladder (OAB) is based on lower urinary tract symptoms and the effect these have on the person's daily life, and excluding other pathology or infection that may be causing the symptoms. This article discusses the assessment of women presenting with lower urinary tract symptoms, including the investigations necessary to diagnose OAB in the primary care setting. Some of these investigations can be performed by practice nurses or GPs, however for some patients referral to a community continence adviser may be appropriate as he or she will have more specialised knowledge and skills. This article also discusses further investigations that may be performed if it is necessary for the patient to be referred to secondary care.

Defining overactive bladder

According to Haylen *et al* (2010), OAB is characterised by urinary urgency with or without urgency incontinence, usually with frequency and nocturia, and in the absence of urinary tract infection or other obvious pathology. This definition was established following a consensus report by the International Urogynecology Association and the International Continence Society, defining standardised terminology for female pelvic floor dysfunction. The report defines urinary urgency as 'a sudden, compelling desire to pass urine which is difficult to defer' and urgency incontinence as 'involuntary loss of urine associated with urgency'. Increased daytime urinary frequency is defined as micturition that 'occurs more frequently during waking hours than previously

deemed normal by the woman', and nocturia as the 'interruption of sleep one or more times because of the need to micturate. Each void is preceded and followed by sleep' (Haylen *et al* 2010).

There are two categories of OAB: OAB dry and OAB wet. People with OAB wet experience urgency urinary incontinence, and those with OAB dry do not experience urinary incontinence. Coyne *et al* (2012) suggested that women with symptoms of OAB can usually distinguish between a normal urge or desire to pass urine and urgency, suggesting that urinary urgency is a continuum where sensations can increase or decrease in severity.

Prevalence of overactive bladder

A population-based survey in Europe showed that the overall prevalence of OAB symptoms in men and women aged 40 and over was 16.6% (Milsom *et al* 2001). OAB is a chronic long-term condition. In a study of 174 women aged 18-75 diagnosed with idiopathic detrusor overactivity in the UK, 88% of women had persisting OAB symptoms lasting ten years or more (Garnett *et al* 2009). Reeves *et al* (2006) suggested that the prevalence of OAB in the UK will rise by 24% over the next 20 years because of the ageing population.

OAB is a distressing problem that can significantly affect a woman's quality of life by constraining her social, physical, occupational and sexual activities. Despite an improvement in diagnosis and treatment and increased awareness, OAB remains under-reported as many people may be reluctant to discuss the condition with their healthcare provider or family (Abrams *et al* 2000).

TABLE 1

Types of incontinence

Type	Definition
Stress urinary incontinence	Involuntary leakage of urine on effort or exertion, or on sneezing or coughing.
Urgency incontinence	Involuntary leakage of urine associated with urgency.
Mixed urinary incontinence	Involuntary leakage of urine associated with urgency as well as exertion, effort, sneezing or coughing.
Nocturnal enuresis	Loss of urine during sleep.
Overflow incontinence	Involuntary leakage of urine associated with poor bladder emptying.
Functional incontinence	Urinary incontinence where no organic cause can be found. May occur as a result of cognitive and physical factors.
Postural urinary incontinence	Involuntary loss of urine associated with change of body position, for example rising from a seated or lying position.
Continuous urinary incontinence	Continuous involuntary loss of urine.
Insensible urinary incontinence	Leakage of urine where the woman has been unaware of how it occurred.
Coital incontinence	Involuntary loss of urine with coitus. May occur with penetration or intromission, or during orgasm.

(Haylen *et al* 2010)

Assessment

Guidelines from the National Institute for Health and Care Excellence (NICE) (2006) on the management of urinary incontinence in women emphasise the importance of a comprehensive initial assessment to establish the type of incontinence and to rule out infections or other causes of symptoms. Gerrits *et al* (2008) revealed that most women who presented to GPs with urinary incontinence were not managed according to NICE (2006) guidelines, and one of the main reasons for this was lack of time during the clinical encounter. To overcome this problem, primary care clinicians may make use of the services provided by continence specialist nurses. These nurses provide a comprehensive assessment of patients with continence needs, including the effect on their family and carers and, if applicable, will implement conservative and pharmacological management plans.

The DH's (2000) guidance on good practice in continence services suggested integral components that should be performed during a routine continence assessment, and this is discussed in the following text.

Urological symptoms

Women with OAB may present with many symptoms, including daytime frequency, urgency, urgency incontinence, nocturia and nocturnal enuresis. Although these are the most common symptoms associated with OAB, there are many other types of incontinence that women may experience (Table 1). The onset of urinary symptoms and their severity should be recorded. Some women might also describe mixed symptoms of OAB and stress incontinence. For these women, the most troublesome symptom should be treated first. It is important to assess how symptoms are affecting quality of life and if further assessment and treatment are required. Examples of relevant history-taking questions for patients with possible OAB are listed in Box 1 (McCrimmon 2005).

Medical history

It is important that a complete medical history (gynaecological, obstetric, surgical and neurological) is taken. Assessment of the individual's mobility, manual dexterity, hearing, eyesight and mental alertness should be performed (DH 2000). For example, reduced dexterity may mean that individuals cannot get their clothing unbuttoned quickly, so improving access to the toilet and suitable clothing can be helpful. In addition, these assessments may help in the planning of suitable therapies and in meeting patients' additional needs. The presence of coexisting conditions that may affect bladder function and cause increased urgency and frequency need to be considered (Box 2).

Medication history

Many medications can exacerbate symptoms of OAB. A review of the patient's concurrent medications should be undertaken. For example, taking diuretics regularly may increase urinary frequency. Alpha blockers cause relaxation of the striated muscle of the urethral sphincter, causing urinary leakage. Parasympathomimetics increase the contractility of the detrusor muscle and may exacerbate symptoms of OAB (Rosenberg 2007). Medications that might cause or exacerbate symptoms of urinary incontinence are listed in Table 2.

Physical examination

An abdominal and vaginal examination should be performed and if indicated, a rectal examination should be carried out. The presence of pelvic organ prolapse, for example a cystocele, may cause urinary urgency and frequency as it drags on the trigone and causes messages of bladder fullness to be sent to the brain (Getliffe and Dolman 2003).

Performing a bimanual examination of the vagina and abdomen will help to rule out pelvic masses, for example ovarian cysts, fibroids and uterine enlargement, which can also cause urinary symptoms. For post-menopausal women with an atrophic vagina and symptoms of OAB, oestrogen deficiency may be a contributory factor in their symptoms (Parsons and Cardozo 2004). Treatment with topical vaginal oestrogens may resolve symptoms (Cardozo *et al* 2004).

A rectal examination is indicated where faecal impaction may be suspected as a contributory factor, or if the woman reports symptoms of faecal urgency or anal incontinence. Recommendations for the physical examination of patients with urinary incontinence are listed in Box 3.

Urinalysis

Urinalysis could indicate the presence of serious disease, for example renal disease, biliary disease or malignancy (Steggall 2007). Testing should be undertaken to rule out the presence of an underlying urinary tract infection, which can cause symptoms of frequency, urgency and incontinence. Lower urinary tract symptoms can be exacerbated or caused by a bacterial infection, and effective treatment with appropriate antibiotics may resolve the symptoms. In some situations, such as investigating a patient with recurrent urinary tract infections, it is necessary to request cultures for organisms such as *Mycoplasma hominis*, *Ureaplasma urealyticum* and *Chlamydia trachomatis*.

Bladder diaries

Bladder diaries can aid evaluation of patients with lower urinary tract symptoms and voiding dysfunction. They can be used to record time of micturition, voided volume, incontinence episodes, pad use and other information such as fluid intake, and degree of urgency and incontinence (Srikrishna *et al* 2007). A completed bladder diary

BOX 1

History-taking questions for patients with possible overactive bladder

- Do you go to the toilet more than eight times per day?
- Do you wake up more than once per night needing to go to the toilet?
- Do you have to hurry to reach the toilet?
- Do you ever not reach the toilet in time?
- If you leak urine, is it a large amount?

(McCrimmon 2005)

BOX 2

Causes of urinary urgency and frequency

Urological:
- Bladder calculus.
- Bladder tumour.
- Chronic urinary residual.
- Detrusor overactivity.
- Interstitial cystitis.
- Radiation cystitis and/or fibrosis.
- Small capacity bladder.
- Urethral diverticulum.
- Urethral syndrome.
- Urinary tract infection.

Medical:
- Congestive heart failure.
- Constipation.
- Diabetes insipidus.
- Diabetes mellitus.
- Impaired renal function.
- Upper motor neurone lesion.

Gynaecological:
- Cystocele.
- Pelvic mass (fibroids).
- Previous pelvic surgery.

Genital:
- Atrophy.
- Herpes.
- Urethral carbuncle.
- Urethritis.
- Vulvovaginitis.
- Warts.

General:
- Anxiety.
- Excessive fluid intake.
- Habit.
- Pregnancy.

assists history taking, and has been shown to be a valuable and reliable tool in the assessment of micturition patterns (Roe *et al* 2007). Frequency volume charts help to establish which patients are drinking excessively, and their habits relating to fluid intake and toileting. However, these can be difficult to complete for patients with functional and cognitive impairments, and therefore are inappropriate for use with these patients.

Quality of life

Symptom and quality of life scoring is used to quantify the effect of urinary symptoms on patients and provides a measure that can be used to assess treatment outcomes. There are many condition-specific questionnaires that can be used in the assessment of women with urinary incontinence. These include the King's Health Questionnaire, International Consultation on Incontinence Modular Questionnaire (ICIQ), Bristol Female Lower Urinary Tract Symptoms, Overactive Bladder Questionnaire (OAB-q), Urogenital Distress Inventory and Incontinence Impact Questionnaire (Abrams 2013). The effect of symptoms on quality of life and desire for treatment should be assessed as this will affect concordance and adherence to therapy (Abrams *et al* 2009). Many of these questionnaires can be obtained from the ICIQ homepage (www.iciq.net/index.html).

Post-micturition residual volume

Measurement of post-void residual volume – the amount of urine in the bladder after a voluntary void – is useful to evaluate voiding dysfunction (Kelly 2004). The symptoms of voiding dysfunction can mimic those of OAB, with implications for management; specifically, drug treatments for OAB tend to decrease voiding efficacy and can precipitate urinary retention (Dwyer and Rosamilia 2002). Residual urine volume can be measured using a bladder ultrasound or an 'in and out' catheter.

'Red flags'

Once an initial assessment has been performed, there are some symptoms or findings that warrant referral to secondary care for specialist investigation. Examples of such symptoms or 'red flags' are listed in Box 4, however this is not an exhaustive list.

Treatment pathways

The NICE (2006) guidelines on the management of urinary incontinence in women included a framework of best practice for patients presenting with symptoms of OAB. The framework recommends that following initial assessment, patients with urge or mixed urinary incontinence should receive at least six weeks of bladder retraining as first-line treatment. If this is not

TABLE 2

Medications that might cause or exacerbate symptoms of urinary incontinence

Medication	Effects
Angiotensin-converting enzyme inhibitors	Diuresis, cough with relaxation of the pelvic floor leading to stress urinary incontinence.
Alpha-receptor antagonists	Urethral relaxation and decreased urethral resistance, causing stress urinary incontinence.
Alpha-adrenergic agonists	Increased urethral resistance causing post-void dribbling, straining, hesitancy and urinary retention.
Anti-cholinergics (H1 antihistamines, anti-parkinsonian agents)	Urinary retention, with symptoms of post-void dribbling, straining, hesitancy in urine flow, overflow incontinence and faecal impaction.
Antipsychotics and/or sedatives, hypnotics	Sedative effect, causing confusion, may relax detrusor muscle leading to urinary retention.
Beta-receptor antagonists	Urinary retention.
Caffeine, also theophylline (methylxanthines)	Polyuria and bladder irritation.
Calcium channel blockers	Urinary retention and faecal impaction.
Diuretics	Polyuria, leading to urgency and frequency.
Neuroleptics (chlorpromazine)	Anticholinergic effect and sedation.
Opioids	Urinary retention, sedation, faecal impaction and delirium.
Tricyclic antidepressants	Anticholinergic and alpha-receptor antagonist effects, causing post-void dribbling, straining and hesitancy in urine flow.

(Rosenberg *et al* 2007)

effective, immediate release generic oxybutynin (an antimuscarinic agent) should be used as first-line drug treatment. The NICE (2006) guidelines are in the process of being updated and are expected to be published in September 2013.

In addition, the International Consultation on Incontinence published guidelines on initial and specialised management of female urinary incontinence (Abrams *et al* 2013).

Specialist investigations

For women referred to secondary care for further investigation of OAB symptoms, several diagnostic tests may be performed. Investigations are only valid if targeted at the appropriate population and the risks of invasive treatments must be balanced against the consequences of under-diagnosis.

Tests such as uroflowmetry, urodynamics and cystourethroscopy as well as radiological imaging, for example intravenous urogram and magnetic resonance imaging, may be undertaken to assess for detrusor overactivity and to observe anatomical abnormalities that may affect choice of management.

Uroflowmetry

Uroflowmetry is a non-invasive screening test for voiding difficulties in women with lower urinary tract dysfunction and helps to determine which patients require further investigation (Abrams *et al* 2005). It is a measurement of the urinary flow rate. To perform this test, women void while seated on a commode connected to a flowmeter that records the volume of urine passed per unit time. A post-void residual volume can be measured following this test.

Urodynamics

There are three types of urodynamic tests that can be performed to investigate symptoms of OAB:

- Subtracted cystometry (cystometrogram (CMG)) – measures the relationship between the detrusor pressure and bladder volume on filling, and between the detrusor pressure and urine flow rate on voiding.
- Video urodynamics (voiding cystourethroscopy (VCU)) – measures the same pressure relationships as in subtracted cystometry, but also uses fluoroscopic images to visualise the lower urinary tract.
- Ambulatory urodynamics monitoring is used to investigate detrusor overactivity, where CMG or VCU have failed to replicate the symptoms that are experienced by the patient in her normal environment. It follows the same principles as subtracted cystometry, but under more physiological conditions (for example, patients fill their bladders naturally by drinking) and bladder pressure is assessed over a longer period of time (for example, four hours). It also aims to reproduce the patients' day-to-day activities.

BOX 3

Recommendations for the physical examination of patients with urinary incontinence

General health:
- Observe mobility and dexterity and any other health problems, including obesity and mental status.

Abdominal/flank examination:
- Check the abdomen for masses, bladder distention and relevant surgical scars.

Pelvic examination:
- Examine the perineum and external genitalia, including tissue quality and sensation.
- Examine the vagina (half-speculum) for prolapse.
- Carry out bimanual pelvic and anorectal examination for pelvic mass, pelvic muscle function, faecal impaction, anal tone and haemorrhoids.
- Conduct stress test for urinary incontinence.

Simple neurological examination
- Assess function of lumbosacral spinal cord by testing feet for normal and equal strength.
- Test for sharp and dull sensations around the thighs.
- Test sensation of perianal skin.

(Adapted from Scientific Committee of the First International Consultation on Incontinence 2000, Abrams *et al* 2010)

BOX 4

'Red flags' warranting referral to secondary care for specialist investigation
- Failed or previous continence surgery.
- Complex symptoms, such as a combination of storage and voiding symptoms.
- Suspected neurological disease.
- Voiding difficulties.
- Recurrent lower urinary tract infections.
- Visible haematuria, or microscopic haematuria if aged 50 and over.
- Symptomatic urogenital prolapse.
- Urogenital atrophy.
- Failure of conservative management.
- Persistent bladder or urethral pain.
- Suspected malignant mass arising from the urinary tract.
- Clinically benign pelvic masses.
- Associated faecal incontinence.
- Suspected urogenital fistulae.
- Previous pelvic cancer surgery.
- Previous pelvic radiation therapy.

(National Institute for Health and Care Excellence 2006)

Cystourethroscopy

Cystourethroscopy visualises the inside of the bladder and urethra. It is an invasive but relatively low-risk procedure that can be undertaken for

women of any age as a day case. The choice between a rigid or flexible cystoscope and the anaesthetic used will depend on the individual and the preferences of the operator. During this test, a camera is passed via the urethra into the bladder to visualise the inside of the bladder. The presence of bladder calculi or tumours can be assessed and a biopsy of the lining of the bladder can be performed to rule out chronic inflammation of the urothelium, which can occur in patients with recurrent urinary tract infections and cause symptoms of OAB.

Conclusion

Several investigations can be performed to diagnose OAB in women, and many of these can be performed in primary care by appropriately trained healthcare professionals. It is essential to ensure that a thorough physical examination is completed, a clinical history is obtained and urinalysis is performed to rule out underlying infection or other more serious diseases.

Adherence to NICE (2006) guidance will provide a safe structure of recommended assessments and ensure appropriate initial management in primary care before patient referral to secondary care for more complex investigation. The quality of assessment will be enhanced by the participation of the patient and carers. Therefore, the healthcare professional needs to have good interpersonal skills to foster a trusting relationship with patients and carers, encouraging them to express their feelings and views about their problems NS

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Choosing drug therapies for urge urinary incontinence in women

Angie Rantell

Abstract

The aim of this article is to provide an overview of the current pharmacological treatments used in the management of urge urinary incontinence.

Urinary incontinence is defined as the complaint of involuntary loss of urine (Haylen et al, 2010). Urinary incontinence is a distressing problem that can seriously affect a woman's quality of life by forcing her to alter her social, physical, occupational, and sexual activities (Kelleher et al, 1997; Getliffe and Dolman, 2007; Sinclair and Ramsey, 2011). In 2008, at the Fourth International Consultation on Incontinence (ICI), it was estimated that, of the world's population, 46% of adults (≥20 years) experience lower urinary tract symptoms, 11% have symptoms of an overactive bladder (OAB), 8% have some type of urinary incontinence, and 3% have severe stress urinary incontinence (Abrams et al, 2009). However, only 7–12% of those affected perceive it as a problem (McGrowther et al, 2001). Incontinence in not a disease but a symptom of an underlying condition, and it can often be successfully treated, improved, or better managed (Colley, 2008).

Terminology and prevalence

A consensus report was developed by the International Urogynaecology Association (IUGA) and the International Continence Society (ICS) to ensure that there was a single standardized document describing the terminology for female pelvic floor dysfunction. In the report, urinary urgency was defined as a complaint of a sudden, compelling desire to pass urine, which is difficult to defer. Urge urinary incontinence was defined as the complaint of involuntary loss of urine associated with urgency. Frequency was described as the complaint that micturition occurs more frequently during waking hours than was previously deemed normal by the woman, and nocturia was set as the complaint of interruption of sleep one or more times because of the need to urinate, where each void is preceded and followed by sleep. 'OAB syndrome' is the term used to describe the symptom complex of urinary urgency with or without urgency incontinence, usually with frequency and nocturia, in the absence of urinary tract infection or other obvious pathology. OAB can be broken down into two subcategories: OAB dry and OAB wet. The latter group experience urge urinary incontinence, whereas the former do not.

Urge urinary incontinence is frequently described by patients as an inability to reach the toilet in time, and women suffering from this symptom often restrict their social activities to ensure that they are constantly near a toilet. Urge urinary incontinence can present in different symptomatic forms (e.g. frequent small losses between micturitions or a catastrophic leak with complete bladder emptying).

In 2001, Milsom et al conducted a population based survey across Europe in which 16 776 interviews were performed. They reported that the overall prevalence of OAB in individuals aged 40 years and older was 16.6%, and this increased with age. They also found that frequency was the most commonly reported symptom (85%), while 54% of respondents complained of urgency and 36% urge urinary incontinence.

Assessment and diagnosis

In order to instigate appropriate treatment, it is essential to determine which type of incontinence a patient has. *Table 1* lists the different types of incontinence and their definition according to the ICS–IUGA joint terminology report (Haylen et al, 2010).

Initial assessment should include a full medical history (including gynaecological, obstetric, surgical, and neurological history), abdominal and vaginal examinations, rectal examination (if indicated), completion of a 3-day bladder diary, urinalysis, and measurement of a post-void residual volume. The impact that these symptoms have on quality of life and desire for treatment should also be assessed, as this will affect compliance and adherence to therapy (Abrams, 2009). Guidelines for the management of urinary incontinence in women (National Institute for

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Table 1. Definitions of different types of urinary incontinence in women

Type	Definition
Stress urinary incontinence	The complaint of involuntary leakage upon effort or exertion, or upon sneezing or coughing.
Urge urinary incontinence	The complaint of involuntary leakage of urine associated with urgency
Mixed urinary incontinence	The complaint of involuntary leakage associated with urgency and also with exertion, effort, sneezing, or coughing
Nocturnal enuresis	The complaint of loss of urine occurring during sleep
Overflow incontinence	Involuntary leakage of urine associated with poor bladder emptying
Functional incontinence	Urinary incontinence where no organic cause can be found; may be due to cognitive and physical factors
Postural urinary incontinence	The complaint of involuntary loss of urine associated with change of body position (e.g. rising from a seated or lying position)
Continuous urinary incontinence	The complaint of continuous involuntary loss of urine
Insensible urinary incontinence	The complaint of urinary incontinence where the woman has been unaware of how it occurred
Coital incontinence	The complaint of involuntary loss of urine with coitus; this symptom might be further divided into that occurring with penetration or intromission and that occurring at orgasm

Health and Clinical Excellence (NICE), 2006) place great emphasis on a thorough initial assessment to determine the type of incontinence and to rule out infections or other causes of their urinary symptoms. It may be necessary to treat other diseases in order to resolve a patient's urinary symptoms. *Box 1* lists some of the differential diagnoses for a patient reporting urge urinary incontinence, and it is important to be aware of possible causes including disease outside of the urinary tract (Barber and Toozs-Hobson, 2002).

Conservative management

According to the ICI (2008), following appropriate diagnosis of urge urinary incontinence, all patients should be offered conservative management in the form of bladder retraining (including fluid and lifestyle advice, urge suppression techniques, weight loss, and management of constipation, if appropriate) and pelvic floor physiotherapy as a first-line management option. This also includes complementary therapies (e.g. hypnotherapy and acupuncture), continence devices, and containment products. Conservative management aims to improve central control of bladder function and avoids the side effects of drug treatment, however, motivation and encouragement is required, and there are high relapse rates (Srikrishna, 2007).

Anticholinergic drugs

In general, pharmacological treatment of urge urinary incontinence is based on the treatment of OAB. Anticholinergic drugs (also known as antimuscarinic drugs) are the mainstay of treatment for OAB symptoms. They inhibit the binding of acetylcholine at muscarinic receptors in the detrusor muscle, thereby reducing the contractions of the detrusor muscle and controlling involuntary detrusor contractions without disturbing normal voiding. The aim of these medications is to reduce symptoms of urgency and urge urinary incontinence and improve quality of life. There are seven different anticholinergics currently available on the UK market, and some of these are available in different preparations (e.g. oral immediate-release and extended-release tablets, and one is available through a transdermal delivery system). *Table 2* shows the anticholinergics available, their recommended dosages, and cost per monthly prescription.

NICE recommendations

NICE (2006) recommend that generic immediate-release oxybutynin should be prescribed as first-line pharmacotherapy. Extended-release tolterodine, extended-release oxybutynin, transdermal oxybutynin, darifenacin, solifenacin, or trospium can all be used for those intolerant to oral immediate-release oxybutynin. However, many health professionals disagree with this recommendation. Immediate-release oxybutynin is

Box 1. Differential diagnoses

- Urinary tract infection
- Overactive bladder
- Detrusor overactivity
- Stress incontinence
- Interstitial cystitis
- Renal stone
- Overflow incontinence with retention
- External pressure (pregnancy, fibroids, pelvic mass)
- Secondary to medical condition (diabetes, myeloma)
- Iatragenic (diuretics, other drugs)
- Psychosocial (dementia, physical disability)

associated with significant side effects, and Kelleher et al (1997) found that only 18.2% of patients continued with therapy in excess of 6 months. The NICE guidelines are currently under revision. They are due to be released later this year, and it is predicted that this recommendation will be changed. Tolterodine has come off patent this year and is available as a generic preparation, significantly reducing its cost, and fesoterodine will be added, as it was not released in the UK until after the NICE guidance had been published.

Side effects, cautions, and interactions of anticholinergics

There are many documented side effects to anticholinergic drugs. These include dry mouth, constipation, blurred vision, dry eyes, drowsiness, difficulty in voiding, and skin reactions (Joint Formulary Committee, 2012). Many women discontinue anticholinergic therapy, as they are unable to tolerate these side effects. In some cases it may be necessary to prescribe additional medication to counteract the side effects of anticholinergics (e.g. laxatives to improve constipation or artificial salivary sprays to reduce dry mouth). Patients should be advised that side effects should reduce after a couple of weeks of therapy.

Anticholinergics should be avoided in patients with myasthenia gravis, urinary retention, severe ulcerative colitis, toxic megacolon and used with caution in those with narrow angle glaucoma.

There are several interactions noted with anticholinergics (e.g. antifungals, antivirals, and parasympathomimetics). Each agent's individual product literature should be consulted for specific recommendation about dose reduction or avoidance of certain agents. More information can be found in Appendix 1 of the *British National Formulary*.

Which anticholinergic?

There is no set rule as to which patient will benefit most from a particular anticholinergic. It may be a case of trialing several medications to find the most efficacious and tolerable drug for the individual patient. Women should be educated and counselled about the role of medication. This should include information about the adverse effects, the estimated length of treatment, all available therapies, how medication will improve their symptoms, and how long it may take to notice these differences (Rantell, 2010). This information will assist the patient to make an informed decision about their treatment and improve compliance with treatment. The use of once daily dosing and alternative routes of administration (e.g. the oxybutynin patch, which is associated with rates of side effects comparable to placebo) may also help improve persistence and compliance. Many companies also provide literature

and support programmes (e.g. telephone help lines) to further aid informed decision making and improve compliance.

There is a lack of data with regard to how long patients should take anticholinergics for (Basra et al, 2008). Some women may be on life-long medication for their bladder; however, some may be able to reduce the dose and/or discontinue treatment as their central control and muscle function improves with conservative therapies. If symptoms recur, patients can restart medication or take an immediate-release preparation on an 'as needed' basis. This should be monitored on an individual patient basis and will be dependent on the severity of incontinence and the impact that their symptoms have on quality of life. All women starting a new medication should be reviewed periodically (e.g. after 1 month, 3 months, and 6 months) to assess drug suitability and symptom relief.

Oestrogens

For post-menopausal women, the use of topical vaginal oestrogens has been shown to help with the symptoms of urge urinary incontinence (Cardozo et al, 2004). These can be prescribed either as a cream (e.g. Ovestin®) or as a vaginal tablet (e.g. Vagifem®) and are used two to three times per week (depending on preparation). Vagifem is now licensed for life-long use. As this therapy is given topically, the risks compared with systemic hormone replacement therapy are minimal but may include some local irritation and occasional breast tenderness. Caution should be taken in women with a previous history of an oestrogen-dependent cancer or history of breast cancer, and advice should be sought from their treating consultant before starting a course of therapy.

Alternative drugs for night-time

Tricyclic antidepressants and synthetic vasopressins are used in the management of nocturia and nocturnal enuresis. Desmopressin is effective in reducing the number of nocturnal voids; however, patients should be closely monitored as it can cause fluid retention and hyponatraemia. It is not suitable in patients over the age of 65 years or in those with renal impairmentor cardiovascular disease. Amitriptyline has been shown to

Table 2. Anticholinergic medications available in the UK and their approximate monthly cost

Drug name	Brand name	Dose	Monthly cost
Darifenacin hydrobromide	Emselex®	7.5–15 mg once daily	£20.90
Fesoterodine fumarate	Toviaz®	4–8 mg once daily	£25.78
Oxybutynin hydrochloride	Ditropan®	2.5 mg twice daily to 5 mg four times daily	£5.86–11.60
Oxybutynin hydrochloride (extended release)	Lyrinel® XL	5–20 mg once daily	£13.77–55.08
Oxybutynin hydrochloride transdermal delivery system	Kentera®	1 patch twice weekly	£27.20
Propiverine hydrochloride	Detrunorm®	15 mg once daily to four times daily	£18–54
Propiverine hydrochloride (extended release)	Detrunorm® XL	30 mg once daily	£24.45
Solifenacin succinate	Vesicare®	5–10 mg once daily	£27.62–35.91
Tolterodine tartrate	Detrusitol®	1–2 mg twice daily	£29.03–30.56
Tolterodine tartrate (extended release)	Detrusitol® XL	4 mg once daily	£25.78
Trospium chloride	Regurin®	20 mg twice daily	£26.00
Trospium chloride (extended release)	Regurin® XL	60 mg once daily	£23.05

be effective at reducing the number of enuresis episodes and imipramine has also been reported to improve symptoms (Parsons and Cardozo, 2004). However, these should be used with caution in the elderly owing to cardiac side effects and the increased risk of falls.

Combination therapy

In some cases, women may be on a combination of drugs to help improve their symptoms. It is not uncommon for a post-menopausal women to be on an anticholinergic medication and topical oestrogens, and there are no contraindications associated with this. Some women may also be on an anticholinergic in the morning, a tricyclic antidepressant or synthetic vasopressin at night, and oestrogen without complication. In women with severe urge urinary incontinence, it is possible that they may take two anticholinergics (e.g. an extended-release tablet and a patch or an extended-release tablet with an immediate-release tablet as needed), but this should be used with caution and following recommendation from secondary care.

Conclusions

There are several different pharmaceutical agents to help treat urge urinary incontinence. It is important to remember that these should not just be used as a sole treatment but rather as a package of care including conservative therapies to ensure the best possible outcomes for patients. Treatment should be individualized to each patient, and it is likely that patients will need to try several different drugs before they find the most beneficial and tolerable medication regimen.

Key Points

- Conservative therapies should be first-line therapy for women with urge urinary incontinence
- It is important to ensure that, before starting therapy, patients are educated and counseled about the role of the medication, side effects, and how it will improve their symptoms
- Patients may need to try several different preparations to find the most efficacious and tolerable treatment for their symptoms
- Oxybutynin patches are useful for patients with swallowing difficulties and those who may forget to take medication and rely on carers

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Pharmacological management of overactive bladder in women

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Abstract

Overactive bladder syndrome (OAB) is a chronic long-term condition whose frequency increases with age. Previous articles have shown that OAB is a prevalent condition, with 16.6% of adults over 40 years of age reporting symptoms (Milson et al, 2001). This article aims to provide an overview of the National Institute for Health and Care Excellence (NICE) guidelines CG171 for the management of female urinary incontinence (NICE, 2013). The guidance includes revised recommendations for the pharmacological treatment of OAB and new treatment pathways.

Overactive bladder syndrome (OAB) is the term used to describe the symptom complex of urinary urgency with or without urgency incontinence, usually with frequency and nocturia, in the absence of urinary tract infection or other obvious pathology (Haylen et al, 2010). Prevalence data from Europe found that 16.6% of adults over the age of 40 report symptoms of an overactive bladder and this is seen to increase with age (Milson et al, 2001). OAB is a chronic long-term condition and in a study of 174 women, 88% had persisting OAB symptoms lasting more than 10 years (Garnett et al, 2009).

In September 2013, the National Institute for Health and Care Excellence (NICE) published updated guidelines on the management of female urinary incontinence (CG171). This included revised recommendations for the pharmacological treatment of OAB. This article aims to review and highlight the treatment pathways from the new guidelines and provide prescribing advice for health care providers treating women with OAB in the primary care setting.

Initial assessment

When a women first presents with symptoms of OAB or reports symptoms during a consultation it is imperative that an appropriate assessment is performed to rule out infective causes of symptoms, or other pathology, such as urinary retention, urogenital prolapse and chronic constipation.

Care pathway A in the NICE Guidelines provides a flowchart recommending what should happen at an initial consultation and when to instigate conservative therapies (NICE, 2013). It is recommended that urinalysis is performed for all patients, along with a vaginal and bimanual examination to rule out, for example, prolapse, a pelvic mass or palpable bladder. An assessment of post-void residual urine by either a bladder scan or in and out catheter is also recommended. Bladder diaries and quality of life questionnaires should be utilized to objectify bladder symptoms and it is important to consider poor habits that may be confounding symptoms, such as an excessive fluid intake or not drinking for long periods of time throughout the day, and to assess the impact that the bladder symptoms are having on the individual's quality of life. It is also essential to perform a full medication review, as some drugs may exacerbate urinary symptoms, such as diuretics, antipsychotics, angiotensin-converting enzyme (ACE) inhibitors and calcium channel blockers.

Red flags

Following initial assessment, there are some red flags that indicate immediate referral into secondary care. These include:

- Microscopic haematuria in women aged 50 yearsand over
- Visible haematuria
- Recurrent or persisting urinary tract infection (UTI) associated with haematuria in women aged 40 years and over
- Suspected malignancy arising from the urinary tract, such as a pelvic mass.

Consideration for referral into a specialist service should also be considered for women with the following indications:

- Persisting bladder or urethral pain
- Clinically benign pelvic masses
- Associated faecal incontinence

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- Suspected neurological disease
- Symptoms of voiding difficulty
- Suspected urogenital fistulae
- Previous continence surgery
- Previous pelvic cancer surgery
- Previous pelvic radiation therapy

Conservative management

Care pathway A recommends conservative therapy as the first-line of management for all women with OAB. This should include at least 6 weeks of lifestyle advice (entailing fluid and caffeine reduction, weight loss, smoking cessation) and bladder retraining. In addition, if a patient reports mixed symptoms (OAB and stress incontinence), pelvic floor muscle training should also be offered.

OAB drugs

Antimuscarinic drugs (also known as anticholinergics) are the most commonly used drugs to treat OAB. They work by blocking the muscarinic receptors in the bladder. This reduces the ability of the bladder to contract and affects bladder sensation. In turn, this reduces urinary urgency and the related symptoms of urgency incontinence, frequency and nocturia. The various medications differ in their selectivity for muscarinic receptors and some have additional actions, such as direct smooth muscle effects (NICE, 2013).

General principles when using OAB drugs

Before starting any drug therapy it is important to assess the impact that treatment may have on an individual. NICE report that in this group of women it is important to consider the following:

- The coexisting conditions of the patient (e.g. poor bladder emptying)
- The use of other medication affecting the total anticholinergic load
- Risk of adverse effects.

According to the British National Formulary (BNF) (Joint Formulary Committee, 2014), anticholinergics should be avoided in patients with myasthenia gravis, significant bladder outflow obstruction or urinary retention, severe ulcerative colitis, toxic megacolon, and in gastro-intestinal obstruction or intestinal atony. Caution is also advised in the frail elderly, those with autonomic neuropathy and narrow angle glaucoma and those with reflux oesophagitis due to hiatus hernia. Antimuscarinics can also worsen hypertension, coronary artery disease, congestive heart failure, hypertension, arrhythmias and tachycardia.

There are several interactions noted with anticholinergics, for example antifungals, antivirals, and parasympathomimetics. The individual product literature of each agent should be consulted for specific recommendation about dose reduction or avoidance of certain agents, and more information can be found in appendix 1 of the BNF (Joint Formulary Committee, 2014).

Box 1 lists the common side effects of antimuscarinics (GP notebook, 2014). Care Pathway B from the NICE guidelines outlines all the recommendations of drug treatment for OAB, along with advice on managing patient expectations and follow up.

Box 1. Side effects of antimuscarinics

Common

- Dry mouth with difficulty swallowing and thirst
- Dilation of the pupils with difficulty accommodating and sensitivity to light, such as blurred vision
- Increased intraocular pressure
- Hot and flushed skin
- Dry skin
- Bradycardia followed by tachycardia, palpitations and arrhythmias
- Difficulty with micturition—urinary retention
- Constipation

Rarely

- Fever
- Confusion, mania, hallucinations
- Rashes

(GP notebook, 2014)

Patient education and counselling

One of the new recommendations in the NICE guidelines is in regard to the discussion that should take place to counsel women about therapy. The guidelines highlight the importance of discussing the following points with women:

- The likelihood of success and associated common adverse effects
- The frequency and route of administration
- That some adverse effects, such as dry mouth and constipation, may indicate that treatment is starting to have an effect
- That they may not see the full benefits until they have been taking the treatment for 4 weeks.

Available agents

There are currently seven different antimuscarinic agents available to prescribe in the UK. Some of these are available in different preparations, e.g. immediate release (IR)/extended release (ER) and oxybutynin is available in alternative delivery routes (patch, tablet, elixir, intravesical instillation). *Table 1* lists all the medications available including their brand names, daily doses and costs according to the NHS Drug Tariff (2014) and BNF (Joint Formulary Committee, 2014).

Table 1. Medications available

Drug name	Brand name	Dose	Cost
Antimuscarinics			
Darifenacin hydrobromide	Emselex	7.5 mg od	£25.48 (28 tabs)
Fesoterodine	Toviaz	4–8 mg od	£25.78 (28 tabs)
Oxybutynin hydrochloride	Ditropan	2.5 mg bd–5 mg tds	£4.71 (max)
Oxybutynin hydrochloride ER	Lyrinel XL	5-20 mg od	£13.77–27.54 (30 tabs)
Oxybutynin hydrochloride tds	Kentera	1 patch twice weekly	£27.20 (8 patches)
Propiverine hydrochloride	Detrunorm	15 mg od–tds	£18.00 (56 tabs)
Propiverine hydrochloride ER	Detrunorm XL	30 mg od	£24.45 (28 tabs)
Solifenacin succinate	Vesicare	5–10 mg od	£27.62–35.91 (30 tabs)
Tolterodine tartrate ER	Detrusitol XL	4 mg od	£25.78 (28 caps)
Tolterodine tartrate	Detrusitol	1–2 mg bd	£29.03–30.56 (56 tabs)
Trospium chloride	Regurin	20 mg bd	£26.00 (60 tabs)
Tropsium chloride ER	Regurin XL	60 mg od	£23.05 (28 caps)
Beta-3-adrenoceptor agonist			
Mirabegron	Betmiga	50 mg od (in moderate to severe renal impairment 25 mg od)	£29.00 (30 tabs)

ER, extended release; XL, extended release; od, once daily; tds, three times per day; bd, twice daily. NHS Drug Tariff, 2014; Joint Formulary Committee, 2014.

Which drug—which patient?

NICE recommendations for drug choices have been developed based on efficacy and tolerability data from the clinical trials of each drug and a cost effectiveness analysis. For first-line therapy it is suggested to offer women either oxybutynin immediate release (IR), tolterodine IR or darifenacin.

If the first treatment for OAB is not effective or well tolerated, it is recommended to offer another drug with the lowest acquisition price. For those unable to tolerate oral medication, a transdermal patch should be offered. There are very few studies comparing antimuscarinics head to head. NICE recommend that the choice of a second-line therapy is based on the lowest acquisition price alone. However, therapy often needs to be tailored to patients needs and not every antimuscarinic will be suitable for all. Further information about each of the licensed medications and their efficacy and tolerability can be found in the full version of the NICE guidelines (2013).

Table 2 lists each of the antimuscarinics and some of the main advantages and disadvantages of each drug. (Please note that this is an observation and does not appear in any clinical guideline or recommendation).

Do antimuscarinics work?

A systematic review was performed by Herbison et al (2003) to determine the effectiveness of antimuscarinic drugs for the treatment of OAB. It reported that although there were statistically significant differences between antimuscarinic drugs and placebo, the effect was small and may be of questionable clinical significance. However, a report by Hartmann et al (2009) reviewed the evidence on the treatment of OAB, urgency urinary incontinence (UUI) and related symptoms, and found that even though treatment effects were quite modest, health-related quality of life (HRQL) and treatment satisfaction measures suggest that such improvements can be important to women. Jonas (2007) suggested that what matters to patients when seeking treatment for OAB goes beyond symptoms, bother and discomfort affect their satisfaction and what matters most to an individual patient is the perceived value of treatment.

Persistence and compliance

Compliance with antimuscarinic medication has always been a concern. A systematic review of persistence and adherence to antimuscarinic therapy was conducted in 2011 (Sexton et al, 2011). They found that in 12-week clinical trials, rates of discontinuation ranged from 4–31% and in every day clinical practice from 43–83% within the first 30 days

Table 2. Advantages and disadvantages of antimuscarinic treatments

Drug	Advantages	Disadvantages
Oxybutynin IR	Flexible dosing, rapid onset of action, cheap	Persistence limited by dry mouth (up to 80% of patients)
Oxybutynin ER	Flexible dosing	Cognitive impairment
Oxybutynin TDS	Placebo rate of side effects	15–20% rate of pruritus
Tolterodine IR	Cheap	Not as efficacious as ER
Tolterodine ER	Well-tolerated	Single dose
Solifenacin	Superior efficacy to tolterodine ER	High rate of dry mouth at dose of 10 mg
Darifenacin	Low rate of cognitive impairment	High rate of constipation
Trospium	Does not cross blood-brain barrier	No comparative data
Propiverine	Well-tolerated	Efficacious only for frequency
Fesoterodine	Flexible dosing, high dry rates (64%)	High rate of dry mouth at 8 mg

ER, extended release; IR, immediate release; tds, three times per day. Please note that this is an observation and does not appear in any clinical guideline or recommendation

of treatment with rates rising over time. It was reported that over half of patients never refill their initial prescription and the most common reason was concern about the balance between the efficacy and tolerability of the antimuscarinic agents. Sear et al (2010) designed a study to see if patients who do not pay for medication were more likely to adhere to therapy. However, 35% of patients still did not refill a prescription for antimuscarinic medication. Once daily dosing may help to improve compliance to therapy and ensuring women are fully counselled and treatment expectations are managed appropriately can also help.

Follow up and review

The new NICE guidelines recommend that all women should be:

- Offered a face-to-face or telephone review 4 weeks after the start of each new OAB drug treatment. The woman should be asked if she is satisfied with the therapy
- If improvement is optimal, treatment should be continued
- If there is no, or suboptimal, improvement or intolerable adverse effects the dose should be changed or an alternative OAB drug tried and reviewed again 4 weeks later
- A review should be offered before 4 weeks if the adverse effects are intolerable
- Referral to secondary care should be offered if the woman does not want to try another drug, but would like to consider further treatment, or if drug treatment is not successful.

For those women who are well-managed on long-term medication it is advised to perform a medication review annually, or every 6 months for those over 75 years old.

Alternatives to antimuscarinics

There will be a group of patients who are unable to have antimuscarinics due to contraindications or due to intolerable side effects. Mirabegron (Betmiga®) is a beta-3-adrenoceptor agonist. It works by activating the beta-3-adrenoceptors causing the bladder to relax, which helps it to fill and also to store urine (NICE TA 290, 2013).

NICE recommends that it is used as an option for treating the symptoms of OAB for people in whom antimuscarinics are contraindicated or clinically ineffective, or have unacceptable side effects. The standard dosage is 50 mg once daily, however, in patients with moderate to severe renal impairment, a 25 mg daily dose is recommended. It is not recommended in patients with severe uncontrolled hypertension and should be used with caution in patients with congenital or acquired QT prolongation. Common side effects are urinary tract infection and tachycardia. A monthly prescription will cost £29 (NHS, 2014).

Conclusion

The updated NICE guidelines provide health care providers with more useful pathways for the drug treatment of OAB. Although there is still ambiguity surrounding the choice of a second-line therapy, it is important to remember that there is no 'one size fits all' treatment. It is often a case of 'trial and error' to find a therapy that is both efficacious and tolerable for patients and it may take several attempts to find the right medication (and will depend on

Key Points

- When a women first presents with symptoms of overactive bladder syndrome (OAB) or reports symptoms during a consultation it is imperative that an assessment is performed to rule out infective causes of symptoms, or other pathology, including 'red flags'
- Conservative management should be the first-line treatment for OAB
- Antimuscarinic agents are the most commonly used drug treatments in the UK
- For first-line therapy it is suggested to offer women either oxybutynin immediate release (IR), tolterodine IR or darifenacin
- All women should be offered a face-to-face or telephone review 4 weeks after the start of each new OAB drug treatment
- Mirabegron is an alternative to antimuscarinic drugs

what is available in your local formulary). If patients are counselled appropriately and expectations are managed accordingly, then this does not affect patient satisfaction and adherence to therapy. However, if this is not the case some women may become disillusioned with therapy and become non-compliant or rely on alternative coping strategies (e.g. pads, restriction on activities) to manage their symptoms.

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Understanding urinary incontinence in women

Urinary incontinence is a common condition in women. Angie Rantell explores the types of incontinence and how to manage them in primary care

Urinary incontinence (UI) is estimated to affect between 17–40% of women in the UK (Hunskaar et al, 2004; Irwin et al, 2006). UI is more prevalent than asthma, epilepsy or dementia (All Party Parliamentary Group (APPG), 2013). According to the International Continence Society/International Urogynaecology Association (ICS/IUGA), the symptom of urinary incontinence is defined as the complaint of involuntary loss of urine (Haylen et al, 2010). UI is associated with reduced quality of life, higher rates of depression, reduced work productivity and decreased enjoyment of sexual activity (Coyne et al, 2008).

This article aims to discuss the common types of UI symptoms that women may report, detailing what an assessment should entail and what investigations should be performed in the primary care setting. Conservative treatment options will also be covered as well as referral recommendations and relevant national policies.

Urinary incontinence symptoms

Lower urinary tract symptoms (LUTS) is an umbrella term for any symptoms that can affect the ability of the bladder to store or empty urine. The ICS/IUGA joint committee has divided the definitions of UI into the eight subtypes below, based on when the symptoms occur (Haylen et al, 2010):

- Stress urinary incontinence (SUI)—complaint of involuntary loss of urine with effort or physical exertion or on sneezing or coughing
- Urgency urinary incontinence (UUI)—complaint of involuntary loss of urine associated with urgency (a sudden compelling desire to pass urine which is difficult to defer)
- Mixed urinary incontinence (MUI)—complaint of involuntary loss of urine associated with urgency and also with effort or physical exertion or on sneezing and coughing
- Postural urinary incontinence—complaint of involuntary loss of urine associated with change of body position, e.g. rising from a seated or lying position
- Nocturnal enuresis (NE)—complaint of involuntary loss of urine that occurs during sleep
- Continuous urinary incontinence—complaint of constant involuntary loss of urine
- Insensible urinary incontinence—complaint of urinary incontinence where the women has been unaware of how it occurred
- Coital incontinence—complaint of involuntary loss of urine with coitus. This symptom can be further divided into that occurring with penetration or intercourse and that occurring at orgasm.

The most prevalent types of UI are SUI, UUI and MUI. UUI and MUI are often associated with overactive bladder (OAB). This is defined as urinary urgency, with or without urgency incontinence, in the absence of infection or any other obvious pathology. It is considered a symptom complex and not a diagnosis.

Disclosure of symptoms

Women often first disclose urinary symptoms to primary care providers during a general examination or a visit for another health problem. Women typically seek help when their symptoms have intensified or are causing worry, when a desire for treatment trumps potential embarrassment, and when they feel comfortable with a health professional (Welch et al, 2011). A recent study by Cooper et al (2014) performed a cross-sectional postal evaluation of all female patients aged over 21 years registered at a single medical practice in the UK. They found that 40% of respondents suffered from UI, which caused significant problems in 8.5%; however, only 17% had sought professional help. This was due to perceptions that UI was part of the natural ageing process and low expectations of successful treatment. Health professionals in primary care are in the ideal position to not only promote health and good bladder habits but also to encourage women to

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Key words: urinary incontinence, pelvic floor, quality of life, referral and consultation

Table 1. Transient causes of incontinence

Delirium
Infection
Atrophic vaginitis
Pharmaceutical agents
Psychological disorders
Excess of urine output
Restricted mobility
Stool impaction

Table 2. Drugs that cause incontinence

Antipsychotics
Antidepressants
Alpha adrenergic agonists
Calcium-channel blockers
Alpha-antagonists
Diuretics
Sedative-hypnotics
Parkinson's disease drugs

disclose symptoms, for example by asking questions about bladder symptoms when women attend for routine smear tests, postnatal checks etc. Effective communication skills are paramount when discussing these sensitive issues with women.

Initial assessment and investigation

UI is a symptom, not a disease, so it is important to ensure that a full assessment is undertaken to rule out transient causes (*Table 1*), underlying pathophysiology, e.g. abdominal mass, or whether the UI is as a result of medications (*Table 2*).

A full past medical, surgical, gynaecological, obstetric, neurological and pharmaceutical history should be taken. All women should undergo a vaginal examination to identify any excoriation of the perineum and identify obvious prolapse. If appropriate training has been received, an assessment of pelvic floor contraction should be performed at the same time.

A urine dipstick test should be undertaken in all women presenting with UI (National Institute for Health and Care Excellence (NICE), 2013a). Urine should be sent away for culture if any abnormalities are detected. Women reporting voiding difficulties or those who have a palpable bladder on examination should also have a measurement of residual urine either by bladder scan or in and out catheter.

Bladder diaries should be completed by women for 3 days so that an objective assessment of toileting habits, fluid intake, and patterns to UI can be reviewed. A bladder diary can be useful. It is important to remind women that the diary also needs to be completed overnight if they wake to void.

Table 3. Essential components of a continence assessment

Review of symptoms and their effect on quality of life
Assessment of the patient's desire for treatment and possible alternative management
Examination of the patient's abdomen for palpable mass or retention of urine
Examination of the perineum to identify prolapse, excoriation and assess pelvic floor contraction
Rectal examination to exclude faecal impaction
Urinalysis to exclude urinary tract infection
Assessment of manual dexterity
Assessment of the patient's environment—access to the toilet
Use of a bladder diary/frequency/volume chart/bladder scan
Identification of conditions that may exacerbate the patient's incontinence—medication, coughs, drinking habits

From: DH, 2000

In 2000 the Department of Health published guidance on Good Practice in Continence services. *Table 3* notes the key components of a continence assessment.

Red flags

According to NICE (2013a) guidelines for female UI the following symptoms require urgent referral to specialist services:

- Visible haematuria
- Microscopic haematuria in women aged 50 years and over
- Recurrent or persisting UTI associated with haematuria in women aged 40 years and over
- Suspected malignancy—mass arising from the urinary tract.

Considerations for immediate referral to a specialist service include:

- Persisting bladder or urethral pain
- Clinical benign pelvic masses
- Associated faecal incontinence
- Suspected neurological disease
- Symptoms of voiding difficulty
- Suspected urogenital fistulae
- Previous continence surgery
- Previous pelvic cancer surgery
- Previous pelvic cancer radiation.

National guidelines

NICE revised guidelines for the management of female urinary in continence in 2013. The guidelines suggest that following assessment women should be categorised as reporting either SUI, UUI or MUI. All should receive lifestyle interventions and pelvic floor muscle training. Those with OAB should also receive bladder retraining. These conservative measures should be tried for at least 6–12 weeks. This is similar to the initial management algorithm set out by the 5th International Consultation on Incontinence (Abrams et al, 2013) as shown in *Figure 1*.

Lifestyle interventions

Women should be advised on the following points:

- Aim to drink 1.5 litres/day; they may need more if they are overweight, exercising or if it is hot (drinking excessive volumes will increase symptoms of frequency and urgency; however, inadequate fluid intake leads to strong,

concentrated urine which irritates the bladder and can contribute to voiding small, frequent volumes of urine)

- Try to spread out their drinking throughout the day
- Avoid drinking late at night (stop drinking 2 hours before bed)
- Weight loss (if needed)—weight loss in moderately obese women has been shown to reduce urgency and number of incontinence episodes (Subak et al, 2005; Wing et al, 2010)
- Stop smoking (nicotine irritates the bladder)
- Avoid constipation—women who report straining at stool are 1.7 times more likely to report urgency (Spence-Jones et al, 1994)
- Stop drinking fluids that irritate the bladder: e.g. caffeine (tea, coffee, green tea, hot chocolate)—women should be advised to have no more than 100 mg of caffeine per day (approximately one cup of coffee) (Bryant et al, 2002); fizzy drinks including sparkling water; artificial sweetener; citrus fruit juices; blackcurrant juice; alcohol (especially white wine); nettle and fennel tea; tomatoes can also irritate the bladder
- Drink: water, diluted fruit juice, milk, fruit tea or herbal teas (such as mint, chamomile or red bush), which cause less irritation to the bladder.

Bladder retraining

Bladder retraining involves a programme of patient education and a scheduled voiding regime. The goals of bladder training are to normalize urinary frequency, improve control over bladder urgency, increase bladder capacity, decrease incontinence episodes, prolong voiding intervals and improve the patient's confidence in bladder control. This is achieved through teaching patients urge-suppression techniques, such as distraction, curling toes or perineal pressure, for example (Wyman et al, 2009). There are many different methods of urge suppression and strategies that can be

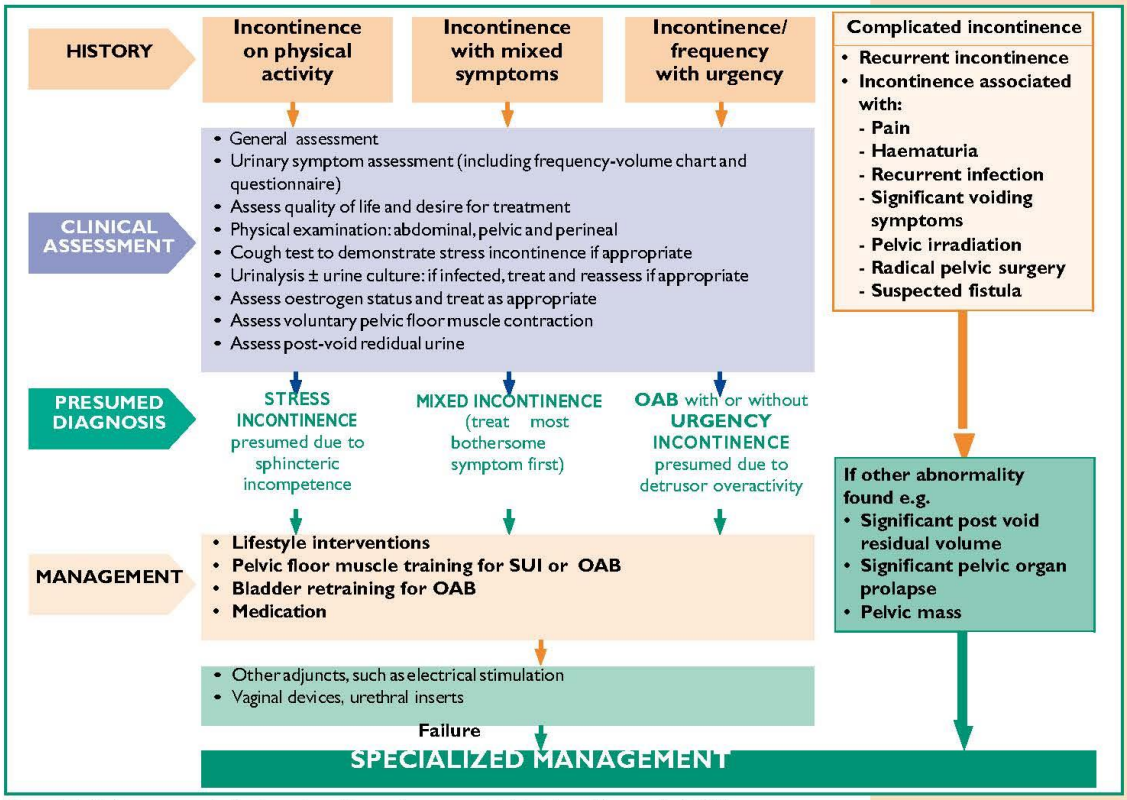

Figure 1. Initial management of urinary incontinence in women. Adapted from Abrams et al, 2012

adopted. Burgio (2011) recommends that when the urge strikes:

- Stop and stay still. Do not rush to the toilet
- Sit down if you can
- Squeeze your pelvic floor muscles quickly 3–5 times and repeat as needed
- Relax the rest of your body. Take a deep breath
- Concentrate on suppressing the urge
- Wait until the urge calms down
- Walk to the bathroom at a normal pace
- If the urge returns on the way to the bathroom, stop and repeat.

This process can be combined with bladder training and delayed voiding to ultimately expand the voiding interval and bladder capacity.

The mechanism by which bladder training works is not clear; however, it is thought to improve central control of the bladder. It has been reported to reduce the number of incontinence episodes in 50–80% cases (Roe et al, 2007). However, bladder retraining takes time and motivation and there is currently no consensus on the optimal regimen.

Pelvic floor muscle training (PFMT)

Pelvic floor muscle training (PFMT) is recommended not only for women with SUI but also for those with UUI or MUI. It involves exercises designed to improve the function of pelvic floor muscles. Women should be advised to perform at least eight contractions three times a day to improve the muscle strength. A digital vaginal examination should be undertaken to confirm that the women is contracting the pelvic floor correctly. For individuals who have trouble identifying and contracting the pelvic floor muscles, biofeedback or electrical stimulation may be useful and women can be referred to a specialist physiotherapist for this.

Further information for patients on bladder retraining and PFMT can be found on the Bladder and Bowel Foundation website: www.bladderandbowelfoundation.org.

Drug treatment of incontinence

Drug treatment for UI is mainly tailored towards the treatment of women with OAB or UUI. The most commonly used agents are anticholinergics or antimuscarinics. These block the cholinergic receptors thus reducing the contractions of the bladder wall. This reduces the need to go to the toilet and

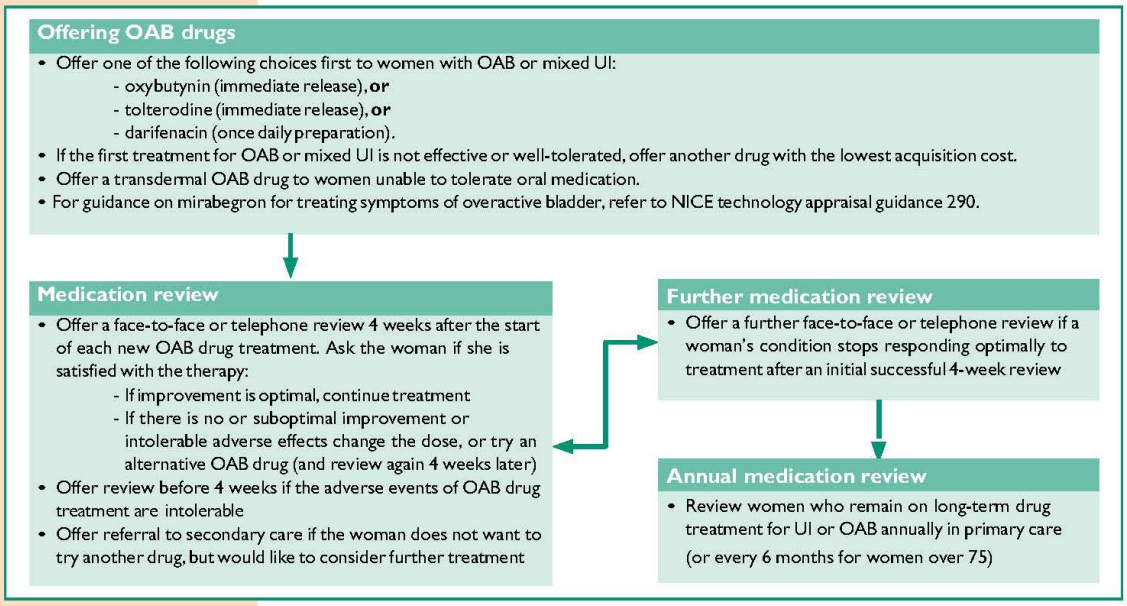

Figure 2. Recommendations for management and follow-up. OAB, overactive bladder. Adapted from NICE, 2013a

decreases the number of urine leaks. There are several different medications available (oxybutynin, tolterodine, solifenacin, fesoterodine, darifenacin, trospium chloride and propiverine) and these are available in a variety of immediate-release and extended-release preparations and different routes of administration including tablets, patches and elixirs. The NICE CG171 Pathway B (NICE, 2013a) set out recommendations for treatment and follow up (see *Figure 2*).

There has recently been increased concern about the long-term use of anticholinergic medication as one study has shown that long-term use of medications with high anticholinergic loads, for example antihistamines and medication for the bladder have been linked to an increased risk of developing dementia (Grey at al, 2015). This article only mentioned immediate-release oxybutynin, which is known to cause confusion and is not advised in the elderly population, particularly in those who are frail. More evidence is required before current practice is reconsidered.

Mirabegron is a beta-3-adrenoceptor agonist. It works by activating the beta-3-adrenoceptors causing the bladder to relax, which helps it to fill and also to store urine (NICE, 2013b). NICE recommends that it is used as an option for treating the symptoms of OAB for people in whom antimuscarinics are contraindicated, clinically ineffective, or have unacceptable side effects.

Minimum standards of continence care in the UK

In recent surveys by the Royal College of Physicians (2010) and APPG (2013), continence care across the UK has been shown to be variable and in some cases poor. In view of this, the UK Continence Society (UKCS) developed a document to encourage improvements in the standard of continence care across the UK through more robust guidelines for training and service configuration (Rantell et al, 2015). The full document can be downloaded from the UKCS website: www.ukcs.uk.net.

Conclusions

The primary care setting is the ideal environment for the initial assessment and conservative treatment of women with UI. It is important for all health professionals to ensure that they are enquiring about bladder function and actively promoting good bladder health. National guidelines are available to follow to ensure treatment is appropriate. Good communication skills are paramount

to ensure that women feel comfortable when disclosing and discussing sensitive issues such as UI.

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KEY POINTS

- Urinary incontinence can significantly impact on a woman's quality of life
- National guidelines are available to aid in assessment and treatment plans
- Conservative measures should be offered as first-line treatment
- Communication skills and maintaining privacy and dignity are key

Update on pharmacological management of overactive bladder

Angie Rantell

Abstract

Overactive bladder syndrome (OAB) is a chronic long-term condition whose frequency increases with age. Previous articles have shown that OAB is a prevalent condition, with 16.6% of adults over 40 years of age reporting symptoms (Milson et al, 2001). This article aims to provide an overview of the National Institute for Health and Care Excellence (NICE) guidelines CG171 for the management of female urinary incontinence (NICE, 2015). The guidance includes revised recommendations for the pharmacological treatment of OAB and new treatment pathways.

Key words: Overactive bladder syndrome; anticholinergics; Antimuscarinic drugs; conservative therapy

Overactive bladder syndrome (OAB) is the term used to describe the symptom complex of urinary urgency with or without urgency incontinence, usually with frequency and nocturia, in the absence of urinary tract infection or other obvious pathology (Haylen et al, 2010). Prevalence data from Europe found that 16.6% of adults over the age of 40 report symptoms of an overactive bladder and this is seen to increase with age (Milson et al, 2001). OAB is a chronic long-term condition and in a study of 174 women, 88% had persisting OAB symptoms lasting more than 10 years (Garnett et al, 2009).

In November 2015, the National Institute for Health and Care Excellence (NICE) updated its guidelines on the management of female urinary incontinence (CG171), following a more extensive update in 2013. This included revised recommendations for the pharmacological treatment of OAB. This article aims to review and highlight the treatment pathways from the new guidelines and provide prescribing advice for health care providers treating women with OAB in the primary care setting.

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Initial assessment

When a women first presents with symptoms of OAB or reports symptoms during a consultation it is imperative that an appropriate assessment is performed to rule out infective causes of symptoms, or other pathology, such as urinary retention, urogenital prolapse and chronic constipation.

Care pathway A in the NICE guidelines provides a flowchart recommending what should happen at an initial consultation and when to instigate conservative therapies (NICE, 2015). It is recommended that urinalysis is performed for all patients, along with a vaginal and bimanual examination to rule out, for example, prolapse, a pelvic mass or palpable bladder. An assessment of post-void residual urine by either a bladder scan or in and out catheter is also recommended. Bladder diaries and quality of life questionnaires should be utilized to objectify bladder symptoms and it is important to consider poor habits that may be confounding symptoms, such as an excessive fluid intake or not drinking for long periods of time throughout the day, and to assess the impact that the bladder symptoms are having on the individual's quality of life. It is also essential to perform a full medication review, as some drugs may exacerbate urinary symptoms, such as diuretics, antipsychotics, angiotensin-converting enzyme (ACE) inhibitors and calcium channel blockers.

Red flags

Following initial assessment, there are some red flags that indicate immediate referral into secondary care. These include:

- Microscopic haematuria in women aged 50years and over
- Visible haematuria
- Recurrent or persisting urinary tract infection (UTI) associated with haematuria in women aged 40 years and over
- Suspected malignancy arising from the urinary tract, such as a pelvic mass.

Consideration for referral into a specialist service should also be considered for women with the following

indications:

- Persisting bladder or urethral pain
- Clinically benign pelvic masses
- Associated faecal incontinence
- Suspected neurological disease
- Symptoms of voiding difficulty
- Suspected urogenital fistulae
- Previous continence surgery
- Previous pelvic cancer surgery
- Previous pelvic radiation therapy

Conservative management

Care pathway A recommends conservative therapy as the first-line of management for all women with OAB. This should include at least 6 weeks of lifestyle advice (entailing fluid and caffeine reduction, weight loss, smoking cessation) and bladder retraining. Inaddition, if a patient reports mixed symptoms (OAB and stress incontinence), pelvic floor muscle training should also be offered.

OAB drugs

Antimuscarinic drugs (also known as anticholinergics) are the most commonly used drugs to treat OAB. They work by blocking the muscarinic receptors in the bladder. This reduces the ability of the bladder to contract and affects bladder sensation. In turn, this reduces urinary urgency and the related symptoms of urgency incontinence, frequency and nocturia. The various medications differ in their selectivity for muscarinic receptors and some have additional actions, such as direct smooth muscle effects (NICE, 2015).

General principles when using OAB drugs

Before starting any drug therapy it is important to assess the impact that treatment may have on an individual. NICE report that in this group of women it is important to consider the following:

- The coexisting conditions of the patient (e.g. poor bladder emptying)
- The use of other medication affecting the total anticholinergic load
- Risk of adverse effects.

According to the British National Formulary (BNF) (Joint Formulary Committee, 2014), anticholinergics should be avoided in patients with myasthenia gravis, significant bladder outflow obstruction or urinary retention, severe ulcerative colitis, toxic megacolon, and in gastrointestinal obstruction or intestinal atony. Caution is also advised in the frail elderly, those with autonomic neuropathy and narrow angle glaucoma and those with reflux oesophagitis due to hiatus hernia. Antimuscarinics can also worsen hypertension, coronary artery disease, congestive heart failure, hypertension, arrhythmias and tachycardia.

There are several interactions noted with anticholinergics, for example antifungals, antivirals, and parasympathomimetics. The individual product literature of each agent should be consulted for specific recommendation about dose reduction or avoidance of certain agents, and more information can be found in appendix 1 of the BNF (Joint Formulary Committee, 2014).

Box 1 lists the common side effects of antimuscarinics (GP notebook, 2014). Care Pathway B from the NICE guidelines outlines all the recommendations of drug treatment for OAB, along with advice on managing patient expectations and follow up.

Box 1. Side effects of antimuscarinics

Common

- Dry mouth with difficulty swallowing and thirst
- Dilation of the pupils with difficulty accommodating and sensitivity to light, such as blurred vision
- Increased intraocular pressure
- Hot and flushed skin
- Dry skin
- Bradycardia followed by tachycardia, palpitations and arrhythmias
- Difficulty with micturition—urinary retention
- Constipation

Rarely

- Fever
- Confusion, mania, hallucinations
- Rashes

(GP notebook, 2014)

Anticholinergic load

Patients taking drugs with anticholinergic effects increase their anticholinergic burden or load, defined as the cumulative effect of taking one or more drugs that are capable of developing anticholinergic adverse effects. A systematic review of the effect of medication with anticholinergic properties described 23 studies, which showed significant decline in cognition (Fox et al, 2014). Three of these studies found there was a significant increase in mortality.

It is presumed that stopping anticholinergic medication will reverse any of the cognitive side effects. However, emerging literature suggests that these effects may be lifelong. In the literature there are up to 11 scoring systems to assess for anticholinergic load. Each drug is given a score which, added together, calculates the burden. Some studies have shown that these scales can act as a predictor for cognitive disorders in elderly people (Tune and Egeli, 1999).

Patient education and counselling

One of the new recommendations in the NICE

Table 1. Medications available

Drug name	Brand name	Dose	Cost
Antimuscarinics			
Darifenacin hydrobromide	Emselex	7.5 mg od	£25.48 (28 tabs)
Fesoterodine	Toviaz	4–8 mg od	£25.78 (28 tabs)
Oxybutynin hydrochloride	Ditropan	2.5 mg bd–5 mg tds	£5.10 (max)
Oxybutynin hydrochloride ER	Lyrinel XL	5-20 mg od	£13.77–£55.08 (30 tabs)
Oxybutynin hydrochloride tds	Kentera	1 patch twice weekly	£27.20 (8 patches)
Propiverine hydrochloride	Detrunorm	15 mg od–tds	£18.00 (56 tabs)
Propiverine hydrochloride ER	Detrunorm XL	30 mg od	£24.45 (28 tabs)
Solifenacin succinate	Vesicare	5–10 mg od	£27.62–35.91 (30 tabs)
Tolterodine tartrate ER	Detrusitol XL	4 mg od	£25.78 (28 caps)
Tolterodine tartrate	Detrusitol	1–2 mg bd	£1.91–2.08 (56 tabs)
Trospium chloride	Regurin	20 mg bd	£5.80 (60 tabs)
Tropsium chloride ER	Regurin XL	60 mg od	£23.05 (28 caps)
Beta-3-adrenoceptor agonist			
Mirabegron	Betmiga	50 mg od (in moderate to severe renal impairment 25 mg od)	£29.00 (30 tabs)

ER, extended release; XL, extended release; od, once daily; tds, three times per day; bd, twice daily
(Joint Formulary Committee, 2016; NHS Drug Tariff, 2016)

guidelines is in regard to the discussion that should take place to counsel women about therapy. The guidelines highlight the importance of discussing the following points with women:

- The likelihood of success and associated common adverse effects
- The frequency and route of administration
- That some adverse effects, such as dry mouth and constipation, may indicate that treatment is starting to have an effect
- That they may not see the full benefits until they have been taking the treatment for 4 weeks.

Available agents

There are currently seven different antimuscarinic agents available to prescribe in the UK. Some of these are available in different preparations, e.g. immediate release (IR)/extended release (ER) and oxybutynin is available in alternative delivery routes (patch, tablet, elixir, intravesical instillation). *Table 1* lists all the medications available including their brand names, daily doses and costs according to the NHS Drug Tariff (2014) and BNF (Joint Formulary Committee, 2014).

Which drug—which patient?

NICE recommendations for drug choices have been developed based on efficacy and tolerability data from the clinical trials of each drug and a cost effectiveness analysis. For first-line therapy it is suggested to offer women either oxybutynin immediate release (IR), tolterodine IR or darifenacin.

If the first treatment for OAB is not effective or well tolerated, it is recommended to offer another drug with the lowest acquisition price. For those unable to tolerate oral medication, a transdermal patch should be offered. There are very few studies comparing antimuscarinics head to head. NICE recommend that the choice of a second-line therapy is based on the lowest acquisition price alone. However, therapy often needs to be tailored to patients needs and not every antimuscarinic will be suitable for all. Further information about each of the licensed medications and their efficacy and tolerability can be found in the full version of the NICE guidelines (2015).

Table 2 lists each of the antimuscarinics and some of the main advantages and disadvantages of each drug. (Please note that this is an observation and does not appear in any clinical guideline or recommendation).

Do antimuscarinics work?

A systematic review was performed by Herbison et al (2003) to determine the effectiveness of antimuscarinic drugs for the treatment of OAB. It reported that although there were statistically significant differences between antimuscarinic

Table 2. Advantages and disadvantages of antimuscarinic treatments

Drug	Advantages	Disadvantages
Oxybutynin IR	Flexible dosing, rapid onset of action, cheap	Persistence limited by dry mouth (up to 80% of patients)
Oxybutynin ER	Flexible dosing	Cognitive impairment
Oxybutynin TDS	Placebo rate of side effects	15–20% rate of pruritus
Tolterodine IR	Cheap	Not as efficacious as ER
Tolterodine ER	Well-tolerated	Single dose
Solifenacin	Superior efficacy to tolterodine ER	High rate of dry mouth at dose of 10 mg
Darifenacin	Low rate of cognitive impairment	High rate of constipation
Trospium	Does not cross blood-brain barrier	No comparative data
Propiverine	Well-tolerated	Efficacious only for frequency
Fesoterodine	Flexible dosing, high dry rates (64%)	High rate of dry mouth at 8 mg

ER, extended release; IR, immediate release; tds, three times per day.
Please note that this is an observation and does not appear in any clinical guideline or recommendation

drugs and placebo, the effect was small and may be of questionable clinical significance. However, a report by Hartmann et al (2009) reviewed the evidence on the treatment of OAB, urgency urinary incontinence (UUI) and related symptoms, and found that even though treatment effects were quite modest, health-related quality of life (HRQL) and treatment satisfaction measures suggest that such improvements can be important to women. Jonas (2007) suggested that what matters to patients when seeking treatment for OAB goes beyond symptoms, bother and discomfort affect their satisfaction and what matters most to an individual patient is the perceived value of treatment.

Persistence and compliance

Compliance with antimuscarinic medication has always been a concern. A systematic review of persistence and adherence to antimuscarinic therapy was conducted in 2011 (Sexton et al, 2011). They found that in 12-week clinical trials, rates of discontinuation ranged from 4–31% and in every day clinical practice from 43–83% within the first 30 days of treatment with rates rising over time. It was reported that over half of patients never refill their initial prescription and the most common reason was concern about the balance between the efficacy and tolerability of the antimuscarinic agents. Sear et al (2010) designed a study to see if patients who do not pay for medication were more likely to adhere to therapy. However, 35% of patients still did not refill a prescription for antimuscarinic medication. Once daily dosing may help to improve compliance to therapy and ensuring women are fully counselled and treatment expectations are managed appropriately can also help.

Follow up and review

The new NICE guidelines recommend that all women should be:

- Offered a face-to-face or telephone review 4 weeks after the start of each new OAB drug treatment. The woman should be asked if she is satisfied with the therapy
- If improvement is optimal, treatment should be continued
- If there is no, or suboptimal, improvement or intolerable adverse effects the dose should be changed or an alternative OAB drug tried and reviewed again 4 weeks later
- A review should be offered before 4 weeks if the adverse effects are intolerable
- Referral to secondary care should be offered if the woman does not want to try another drug, but would like to consider further treatment, or if drug treatment is not successful.

For those women who are well-managed on long-term medication it is advised to perform a medication review annually, or every 6 months for those over 75 years old.

Alternatives to antimuscarinics

There will be a group of patients who are unable to have antimuscarinics due to contraindications or due to intolerable side effects. Mirabegron (Betmiga®) is a beta-3-adrenoceptor agonist. It works by activating the beta-3-adrenoceptors causing the bladder to relax, which helps it to fill and also to store urine (NICE, 2013).

NICE recommends that it is used as an option for treating the symptoms of OAB for people in whom antimuscarinics are contraindicated or clinically

Key Points

- When a women first presents with symptoms of overactive bladder syndrome (OAB) or reports symptoms during a consultation it is imperative that an assessment is performed to rule out infective causes of symptoms, or other pathology, including 'red flags'
- Conservative management should be the first-line treatment for OAB
- Antimuscarinic agents are the most commonly used drug treatments in the UK
- For first-line therapy it is suggested to offer women either oxybutynin immediate release (IR), tolterodine IR or darifenacin
- All women should be offered a face-to-face or telephone review 4 weeks after the start of each new OAB drug treatment
- Mirabegron is an alternative to antimuscarinic drugs

ineffective, or have unacceptable side effects. The standard dosage is 50 mg once daily, however, in patients with moderate to severe renal impairment, a 25 mg daily dose is recommended. It is not recommended in patients with severe uncontrolled hypertension and should be used with caution in patients with congenital or acquired QT prolongation. Common side effects are urinary tract infection and tachycardia. A monthly prescription will cost £29 (NHS, 2014).

Conclusion

The updated NICE guidelines provide health care providers with more useful pathways for the drug treatment of OAB. Although there is still ambiguity surrounding the choice of a second-line therapy, it is important to remember that there is no 'one size fits all' treatment. It is often a case of 'trial and error' to find a therapy that is both efficacious and tolerable for patients and it may take several attempts to find the right medication (and will depend on what is available in your local formulary). If patients are counselled appropriately and expectations are managed accordingly, then this does not affect patient satisfaction and adherence to therapy. However, if this is not the case some women may become disillusioned with therapy and become non-compliant or rely on alternative coping strategies (e.g. pads, restriction on activities) to manage their symptoms.

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Review article

Assessment of the impact of urogenital prolapse on sexual dysfunction

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a r t i c l e i n f o

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a b s t r a c t

Sexual dysfunction is one of the symptoms that motivates women to seek medical help in the manage- ment of urogenital prolapse. Conservative or surgical interventions may be offered to treat the prolapse but the question remains as to whether treatment restores sexual function (SF). This article briefly dis- cusses the assessment of SF in women with a urogenital prolapse and reviews the effect of therapeutic interventions on SF.

Contents

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1. Introduction

Pelvic organ prolapse (POP) is a very common condition, particularly among older women. It is estimated that 50% of women who have children will experience some form of prolapse in later life, but because many women do not seek help the prevalence is unknown [1]. It is generally the symptoms associated with prolapse, such as bladder, bowel and sexual dysfunction, that motivate women to seek medical help and prolapse accounts for 20% of women on the waiting list for gynaecological surgery [2].

Sexual health is defined as 'a state of physical, emotional, mental and social well-being in relation to sexuality; it is not merely the absence of disease, dysfunction or infirmity' [3]. Prevalence studies report that up to 64% of women attending urogynaecology clinics report some form of sexual dysfunction [4] and urogenital pro- lapse is more likely than urinary incontinence to result in sexual inactivity and to be perceived as affecting sexual relations [5]

The aim of this paper is to review the impact that current conservative and surgical therapeutic interventions for the management of POP has on sexual function.

1.1. Pelvic organ prolapse

POPisdefinedprimarilyasanatomicalchange, iethedownward displacement of a pelvic organ or the different vaginal compartments and their neighboring organs [6]. Symptoms include vaginal bulging, pelvic pressure and low backache. Women may also develop prolapse related lower urinary tract symptoms and prolapse related anorectal dysfunction symptoms. Table 1 displays the potential prolapse related sexual dysfunction symptoms that women may report [6].

1.2. Femalesexualfunction/dysfunction

According tothe World Health Organization International Classifications of Diseases—10 (ICD-10), the definition of female sexual dysfunction (FSD) includes 'the various ways in which an individual is unable to participate in a sexual relationship as she would wish' [7]. There are 4 major categories of dysfunction, that is desire, arousal, orgasmic and sexual pain disorders [8]

Suggested areas of pathophysiology that can cause FSD are listed below in Fig. 1 [9].

Gladu reported four causes of FSD: medical illnesses (eg hypertension, diabetes and previouspelvic surgery), psychological illnesses (underlying depression, anxiety), hormonal deficiencies (menopausal changes) or the effects of medications (eg selec- tive serotonin reuptake inhibitors, antidepressants, tamoxifen, etc) [10]. POP can affect several of the areas listed above and as such correction of the POP alone may not improve sexual function if the other causes are not addressed.

Table 1
Sexual dysfunction symptoms.

	Definition
Dyspareunia	Complaint of persistent or recurrent pain or discomfort associated with attempted or complete vaginal penetration
Obstructed intercourse	Complaint that vaginal penetration is impeded. Possible causes include narrowing or a bulge
Vaginal laxity	Complaint of excessive vaginal looseness
Libido – loss or decrease	Complain of loss or decrease of sexual desir

- Mind and age (neurotransmitters, medication)
- Oestrogens and androgens
- Vaginal epithelium and lubrication
- Vaginal blood flow
- Coital incontinence
- Scar tissue / vaginal dimensions
- Neuropathy
- Pelvic floor muscles

Fig. 1. Areas of pathophysiology of sexual dysfunction.

1.3. Urogenital prolapse and urinary incontinence

The relationship between urogenital prolapse and urinary incontinence is well documented, 63.3% of patients with Stress Uri- nary Incontinence (SUI) have co-existing POP and conversely 62.7% of women with POP have co-existing SUI [11]. One explanation for co-existing pelvic floor dysfunction, such as POP and SUI, is that they have shared risk factors, which would thereby increase the risk of both of these conditions [12].

Rogers et al. comparedsexual function in women with and without urinary Incontinence (UI) and/or pelvic organ prolapse (POP) using a validated condition-Specific questionnaire, the Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire (PISQ), and concluded that PISQ scores were significantly lower among women with UI/POP than in those without ($P = 0.003$). Women with UI/POP have poorer sexual function, as measured by the PISQ, and report less frequent sexual activity [13]. In addition, women with UI/POP are more likely to restrict sexual activity for fear of incontinence. Women with POP and UI are more likely to report decreased libido, decreased sexual excitement, and difficulty achieving orgasm during intercourse when compared to women with UI alone [14].

1.4. Assessment

Initial assessment should focus on symptoms experienced by women followed by a detailed medical history with a particu- lar focus on identifying other risk factors eg chronic constipation, collagen disorders (benign joint hypermobility/Elhers Danlos syn- drome), and familial history of prolapse.

Quality of Life questionnaires and symptom specific questionnaires can beusefulin theclinical setting, particularly when women report a variety of bladder, bowel, and sexual dysfunction symptoms. There are many validated questionnaires available eg The King's Health Questionnaire (KHQ), Pelvic organ prolapse symptom questionnaire (POP-S) and the Prolapse and Incontinence Sexual Function (PISQ) questionnaire. The International Consultation on Incontinence(ICI) havedevelopedmodular questionnairesthat are availableand free todownloadto all clinicians athttp://iciq.net/

A vaginal examination should be performed to assess for pro- lapse. There are many different staging and grading systems in the literature but the Pelvic Organ Prolapse Quantification System (POP-Q) is the recommended method. The choice of the woman's position during examination, e.g. left lateral (Sims), supine, stand- ing or lithotomy is that which can best demonstrate POP in that patient and which the woman can confirm as the maximal extent she has perceived e.g. by use of a mirror or digital palpation[6].

Diagnosis is usually clinical and based on history and examination. However, if there are urinary symptoms it may be necessary to consider urinalysis±a midstream specimen of urine (MSU), post-void residual urine volume testing, urodynamic investigations or a renal ultrasound scan. If there are bowel symptoms consider anorectalmanometry, defaecatingproctographyandan endo-anal ultrasound scan. A trans-vaginal ultrasound scan will also help to rule out any pelvic mass that may add to or cause symptoms on

prolapse, particularly in women for whom bimanual examination is sub optimal due to body habitus.

2. Effect of therapeutic interventions

2.1. Management: pelvic floor muscletraining

PFMT is often considered as the first line in management of urogenital prolapse. Ideally, an individualised programme of pelvic floor should be offered by specialist women's health physiotherapists [15] which may include pelvic floor exercises, vaginal examination and advice regarding lifestyle changes. It may also include the use of biofeedback or neuromuscular electrical stimulation.

However, there is no conclusive evidence on the efficacy of PFMT with regards to female sexual dysfunction. In one recent RCT [16], where women were randomised to an intervention group (6 months of PFMT and lifestyle advice) and a control group (lifestyle advice only), no significant change in the number of women being sexually active was reported. There were no significant differences between groups regarding change in satisfaction with frequency of intercourse. Women reporting improvement in sexual function demonstrated the greatest increase in PFM strength and endurance. The POPPY trial [17], a parallel-group, multicentre, randomised controlled trial at 23 centres in the UK, New Zealand, and Australia, was the largest study to investigate the effect of individualised pelvic floor muscle training in women with pelvic organ prolapse. Close to five hundred women were randomised into an individu- alised programme of pelvic floor muscle training or given a prolapse lifestyle advice leaflet. Interestingly, in the short term, i.e. at six months, sexual function did appear to be significantly improved, however this benefit did not last at the end of the year. Therefore, long-term benefit of physiotherapy still needs further investigation.

It could also be postulated that pelvic floor strengthening leads to differential improvements in different domains of sexual function, as in some studies PFMT has been shown to lead to an improvement in sexual desire, performance during coitus and achievement of orgasm with no change was seen in arousal and resolution [18].

Ultimately, sexual function may be at least partially related to strength of the pelvic floor as shown in retrospective review. In this study, women with strong or moderate pelvic floor muscle scored significantly higher on the orgasmic and arousal domains of the female sexual function index (FSFI) than women with weak muscles. In addition, the duration of PFM contraction was correlated with FSFI orgasmic domain and sexual arousal [19].

Although the evidence to support physiotherapy as a manage- ment option in FSD is tenuous it would seem sensible to continue with PFMT as the first line option given the lack of any associated morbidity or mortality with this line of therapy.

2.2. Management: vaginalpessaries

At present there is not a plethora of evidence in published literature detailing the effects of pessaries on sexual function in women with pelvic organ prolapse.

Some data would suggest that, in patients with symptomatic pelvic organ prolapse, desire, lubrication, and sexual satisfaction improvesignificantlywithpessaryuse.Thefindings ofthis prospective study suggestthat vaginalpessaries do not interfere negatively with sexual activity and may even improve sexual function [20].

Another prospectivestudy into patient symptomsshowedasignificant improvement in sexualsatisfaction and frequency of sexual activity with pessary use [21]. In addition, a trial comparing the effectiveness of pessaries and surgery in women with symptomatic pelvic organ prolapse found similar improvement in urinary, bowel, sexual function, and quality of life parameters using both interventions. [22]

Contrary to popularly held belief that sexual activity is likely to be a relative contraindication to long term pessary treatment [23], evidence suggests that sexually active women are more likely to continue wearing their pessary than women who were not sexu- ally active, suggesting that long-term pessary use is acceptable to sexually active women [24].

Consequently, whilstpessaries and surgery appeartohave comparable beneficial effects, in the absence of significant serious morbidity and mortality with pessary this option should discussed with all patientswith urogenital prolapse, including thosewith sexual dysfunction. However, it is important to remember that long term pessary use is not completely free from complications. Up to 56% of patients using pessaries long term are likely to report some complication, including bleeding, extrusion, severe vaginal discharge, pain and constipation [25]. Therefore all women opting for this treatment option should be fully informed about the risks and benefits and the importance of regular change of the pessary.

2.3. Management: surgery

Surgery is often the definitive treatment for urogenital pro- lapse and the lifetime risk of needing surgery is 11%, with 29.2% requiring repeat surgery[2]. Data reporting sexual function follow- ing surgical repair are limited and conflicting. Some studies have shown an improvement [26–28], whilst others have suggested a deterioration in sexual function [29,30].

Pelvic surgery to correct urogenital prolapse may affect sexual function for a number of reasons including narrowing the vagina, reducing lubrication, and because of a risk of urinary incontinence.

2.3.1. Hysterectomy

Hysterectomy has been associated with sexual dysfunction, including dyspareunia as well as anorgasmia [31]. It is postulated that extensive dissection of the pelvic floor is implicated in pelvic floor neuropathy affecting the pudendal nerve, impairing vaginal sensation and orgasm. Recent studieshave shown that cervicalconservation at subtotal hysterectomy does not appear to confer any advantage over total hysterectomy with regards to pelvic organ function. Older reports in literature had suggested a risk of neuropathy associated with removal of the cervix, although there is now considerable evidence that simple abdominal or vaginal hysterectomy does not adversely affect sexual function [32].

2.3.2. Anterior colporrhaphy

Repair of the anterior compartment, particularly in the absence of synthetic mesh augmentation has not been specifically reported to cause impaired sexual function and some studies report an improvement in sexual function following anterior colporrhaphy. [33]

2.3.3. Posterior colporrhaphy

Posterior colporrhapy, particuarlly levator plication, has been also been long implicated as a cause of postoperative dyspareunia. Consequently older studies report alarmingly high rates of dyspareunia as well as apareunia following posterior repair [34–36]. However, the modern approach of site-specific repair of rectoceles has a much lower risk of dyspareunia [37,38]. The use of mesh in theposterior wallhasbeen shown to increase dyspareuniain 63% of women [39] and therefore the use of mesh in any routine posterior repair is ill advised.

Finally, if both anterior and posterior colporrhaphy are performed at the same sitting, particular care needs to be exercised

as this can cause mid-vaginal stenosis secondary to a constriction ring and create de-novo dyspareunia

2.3.4. Apicalsurgery

Vaginal vault prolapse can be corrected either by an abdomi- nal or a vaginal approach. Sacrospinous fixation (SSF) is the most commonly performed vaginal procedure. Sexual function after sacrospinous fixation can be altered either because of pain, vagi- nal narrowing or pudendal nerve injury. Several studies have cited varying impact of SSF on sexual function, either reporting it as maintained, improved or worsened [40–43].

With regards to abdominal sacrocolpopexy, two randomised controlled studies comparing vaginal and abdominal approaches have reported conflicting results. One study found no significant difference in post-operative dyspareunia in either group, although clinically more patients reported dyspareunia in the vaginal group [44]. In contrast, a study performed by Maher et al. found no difference in sexual function between the two groups postop- eratively [45]. Of patients not sexually active preoperatively, 28 and 21% resumed sexual activity postoperatively, and preoperative dyspareunia resolved in 56 and 43% in the abdominal and vagi- nal groups, respectively. Dyspareunia developed de novo in two women in the abdominal and three women in the vaginal group.

2.3.5. Vaginal mesh

The use of synthetic mesh augmentation at the time of repair remains controversial with some studies suggesting increased levelsofpersistent dyspareunia in 50% ofsexually activewomen when compared to native tissue repair [46]. Literature continues to provide conflicting evidence, with a recent retrospective study of over 200 women undergoing vaginal prolapse surgery using a synthetic graft reporting a positive objective and subjective outcome and significantly improvedquality of life at a minimum of 5 year follow-up [47].

However, a randomised controlled trial comparing vaginal repair augmented by mesh with traditional colporrhaphy for the treatment of pelvic organ prolapse found similar rates of de novo dyspareunia in both groups. [16.7% in the mesh group and 15.2% in the no mesh group at 12 months] [48]. Similarly, another randomised study involving ninety-seven patients randomised to colporrhaphy with no mesh and 105 with mesh found that dys- pareunia was statistically significantly lower in the mesh group [49].

2.4. Hormones

For those women that are already post menopausal, urogenital atrophy may cause loss of lubrication and hormonal changes that lead to sexual dysfunction [50]. Treatment of urogenital atrophy with topical vaginal oestrogens can improve quality of life not only for the women but also for her partner [43,51].

Another cause for dyspareunia is poor oestrogenisation of the vaginal epithelium in those women who undergo surgical menopause at the time of a hysterectomy for prolapse. Therefore careful pre-operative counseling is essential with regard to concomitant oopherectomy.

2.5. Psychologicalimpact

Sexual function is related to a woman's self-perceived body image and degree of bother from POP regardless of stage of prolapse therefore sexual function may be more related to a woman's perception of her body image than to actual topographical changes from POP [52].

Because sexual function is complex, the physical changes from surgery might not address the issues contributing to sexual dysfunction preoperatively. These issues, such as desire, other limiting medical conditions, or relationship status, might not be improved after the structural changes of prolapse are addressed [53]. Thorough assessment is essential to understand these underlying issues and ensure that the most appropriate treatment is offered.

3. Conclusions

Sexual dysfunction is a common cause of quality of life impairment and is known to have a high prevalence in women with urogenital prolapse andurinary incontinence. Whilst thecauses are often multifactorial it is important to actively case find and screen women prior to conservative or surgical intervention.

Whilst there is good evidence to suggest that PFMT improves sexual function the evidence supporting the use of vaginal pes- saries and surgical intervention is less robust and long term follow up studies are required to assess the impact of both native tissue repairs and also repairs using synthetic material.

As our understanding of female sexual dysfunction improves our ability to identify women with troublesome symptoms will increase allowing more effective and timely intervention which ultimately should improve the care of patients with urogenital pro- lapse and concomitant sexual dysfunction.

Contributors

AR and SS undertook the review of the literature and were responsible for the content and drafting of the manuscript.

DR provided assistance with the writing, editing and proofread- ing of the manuscript.

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ORIGINAL CLINICAL ARTICLE

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Personal goals and expectations of OAB patients in the UK

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INTRODUCTION: In clinical practice and in research patient-centred outcomes are often utilised to help improve communication between patients and clinicians and to help manage e xpectations from t reatment. However, many of these goals are generic and do not adequately capture the details of day to day life that bother patients the most and that they hope will improve with therapy. This study aimed to understand what are the goals of patients with overactive bladder symptoms in the UK who were taking part in a clinical trial and to assess goalachievement.

METHODS: This was a qualitative analysis of the patients goals recorded using the Self-Assessment Goal Achievement (SAGA) Questionnaire during the UK study assessing flexible dose fesoterodine in adults (SAFINA) trial. Free text patient goals were completed at baseline and an assessment of achievement was performed at the end of treatment. Grounded theory was used to develop themes and sub themes.

RESULTS: Three hundred and thirty-one patients completed the trial and 1137 open ended goals were set. Six themes emerged from the data including, OAB, other LUTS and finishing the task in hand with multiple subthemes noted.

CONCLUSIONS: By assessing and understanding what is important to the patient, it may help to tailor patient care and treatment and improve patient satisfaction.

KEYWORD S

overactive bladder, patient-centred outcomes, patients goals, patient satisfaction

1 | INTRODUCTION

Overactive bladder (OAB) is the term used to describe the symptom complex of urinary urgency with or without urgency incontinence, usually with frequency and nocturia, in the absence of urinary tract infection or other obvious pathology.[1] Prevalence studies report that 12.8% of women over the age of 18 years describe symptoms of OAB.[2] It is a long-term fluctuating condition with up to 88% of sufferers reporting symptoms for more than 10 years.[3] It affects more women than men under the age of 70 but above this age, the prevalence of OAB symptoms are more equal among the sexes.

Many studies have reported the detrimentaleffect of OAB on an individual's quality of life by forcing them to alter their social, physical, occupational and sexua l activities,[4,5] however, it has been difficult to determine the specific aspects of life that are affected and what treatment goals patients wish to achieve with treatment. Schlenk et al. (1998) determined that urinary incontinence (UI) represents one of the most bothersome chronic diseases affecting physical functioning.[6] A recent systematic review on the impact of quality of life of urinary incontinence and overactive bladder concluded that at variance with other chronic conditions, quality of life deterioration in UI or OAB patients is characterised by its hidden and embarrassing nature. This suggests that clinicians need to raise awareness of the impact that these symptoms can have, help patients to improve their self-confidence to report symptoms, as well as, encouraging sufferers to have treatment for their condition to overcome its hidden nature.[7]

In research and clinical practice patient-centred outcomes are often utilised. These were first described by Brubaker and Schull (2005) who coined the term EGGS to facilitate communication about patient-centred treatment outcomes—E expectations, G goal setting, G goal achievement, S satisfaction.[8] It has been reported that positive

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physician—patient communication and setting individualised treatment goals can lead to improved patient satisfaction.[9] Also by allowing patients to set their own goals for treatment, and then to self-assess achievement of those goals may help to capture the effect of OAB and the impact of treatment in a more individualised, patient-centred way than disease specific quality of life questionnaires that are commonly used.[10]

Although goal attainment scoring (GAS) has been used for different conditions, there were no self-completed instruments that would allow patients with lower urinary tract symptoms to proactively capture their treatment goals for discussion with their healthcare provider in routine clinical or research setting, hence the development of the SA GA questionnaire by Brubaker et al.[11] It was designed to improve physician-patient interaction and to allow goal achievement to be assessed in research studies. It has been validated and its clinical value assessed and it has been used in many different research trials for patients with OAB.

The aim of this study was to analyse the goals that patients in a UK clinical trial wished to achieve from treatment for their overactive bladder and to review goal achievement after 12 weeks of therapy using the SA GA questionnaire.

2 | METHODS

The UK study assessing flexible-dose fesoterodine in adults (SAFINA) was a 12 week, multi-centre open label study which recruited 331 adults with OAB at 39 sites in the UK from February 2009 to January 2010.[12] The aim of the study was to evaluate the efficacy and safety of flexible dose fesoterodine and factors associated with dose escalation in subjects with OAB. All subjects were treated with fesoterodine 4 mg once daily for the first 4 weeks and were then given the option to dose escalate up to 8 mg for the next 8 weeks. Treatment was stopped at 12 weeks and subjects were reassessed at 16 weeks.[13] At each visit in the study, patients completed a 3 day bladder diary and multiple questionnaires to identify patient reported outcomes. A preliminary version of the Self–Assessment Goal Achievement (SA GA) questionnaire was included in the study as an exploratory endpoint. Inclusion/exclusion criteria can be found in the main study paper.[12] This study was approved by the appropriate Independent Ethics Committee and conducted in compliance with the ethical principles of the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice Guidelines. Written informed consent was obtained from each subject before entering the study.

The SA GA questionnaire is a patient completed, physician reviewed tool to assess patient's goals for treatment and whether the goals are achieved for subjects suffering from OAB and/or other urinary tract symptoms. The SA GA questionnaire is in two parts. The first questionnaire contains nine fixed goals with a further five open-ended goals. These are reviewed with the clinician in order to assess whether the goals are realistic. The SA GA follow up questionnaire asks the subject to relate the degree of achievement of the original treatment goals set prior to the start of treatment.

This paper specifically examines the open-ended goals that patients chose regarding what they would most like to achieve from therapy. To assess these goals, the responses were analysed thematically based on grounded theory. This theory was first described by Glaser and Strauss in 1976.[14] The idea is that theory is grounded in and emerges from data. Constant comparison is key to the method and in this analysis, all goals were transcribed onto individual cards. Each patient goal was compared with the goals from previous and subsequent subjects. These comparisons gave rise to categories/themes and sub-themes which summarise patient's views. Examples of these comparisons follow: Example 1. 'Reduce the number of times I go at night', 'to sleep through the night', 'better quality sleep', 'to get up less at night' are all examples of patient set goals relating to nocturia, therefore, these were sorted into a subcategory of nocturia and as it is one of the symptoms of OAB, the core category was OAB. Example 2. 'To go on journeys without worrying about toilet', 'to take dog for a walk without needing the loo', ' watch a film without going to the toilet', ' complete a meeting at work without leaving to go to the toilet' are all examples of patients goals relating to specific tasks that they wish to complete, therefore, each individual task was formed as a subcategory while the core category developed was related to finishing the task in hand.

Data saturation was achieved when further set goals could add nothing to what was already know about a category, its properties, and its relationship to the core category.

Goal achievement was graded as follows: did not achieve somewhat achieved, achieved, exceeded expectation and greatly exceeded expectation.

3 | RESULTS

The baseline demographics of subjects are shown in Table 1. The results of the nine fixed goals from the SA GA questionnaire can be found in the paper by Cardozo et al. 2012[12] and are demonstrated in Table 2.

Of the 331 subjects who were assigned to treatment, 1137 open-ended goals were set. The themes and sub-themes

TABLE 1 Baseline demographics and clinical characteristics (n = 331)

Variable	Value
Sex	
Male	68 (20.5)
Female	263 (79.5)
Age (years)	
Mean (SD)	60.3 (12.4)
Range	23–86
Race, *n*%	
White	325 (98.2)
Other	6 (1.8)
Weight (kg)	
Mean (SD)	79.9 (18.4)
Range	51–174
Duration since first diagnosis of OAB (yrs)	
Mean (SD)	7.7
Range	0.1–53.8
Incontinence, *n* (%)	132 (39.9)
Bladder diary variables per 24 h, mean (SD)	
Micturitions	12.8 (3.5)
Nocturnal micturitions	2.7 (1.6)
Urgency episodes	9.1 (4.3)
UUI episodes	2.1 (2.4)

that emerged from the data are listed in Table 3 along with the number of patients expressing that subject as a treatment goal.

All goals were included in the analysis regardless of whether it was thought that these were unrealistic. Examples of what may be considered as unrealistic goals include 'to not have any pain', 'to sneeze without leaking', 'to fully empty bladder' and are discussed below.

Two hundred and fifty-one subjects completed the trial and goal achievement was ranked for all goals set out by subjects and the level of achievement of their personal goals is listed in Table 4.

TABLE 2 Results of fixed SAGA goals reported in the SAFINA study

Saga fixed goal	% Rated 'very important' at baseline
Reduce the sudden need to rush to the bathroom	77
Reduce frequency to the bathroom through the day	66
Reduce my urine leakage	81% of those incontinent at baseline
Reduce difficulty starting or maintaining a urinary stream	12

TABLE 3 List of themes and sub-themes (n = 331)

	Theme	Sub-themes	Number
A)	OAB	Reduce nocturia	156
		Reduce urgency	104
		Reduce frequency	101
		Reduce UUI	86
		Reduce pain	47
		Not have to wear pads	45
		Reduce latchkey urgency	8
B)	Other LUTS	Reduce leakage on coughing	41
		Reduce leakage on exercising	23
		Empty bladder completely	22
		Improve weak stream	8
		Reduce leakage during housework	4
		Reduce leakage when swimming	3
C)	Finishing the task in hand	Car/coach journey without stopping	78
		Shopping trip without finding loo	56
		Walk dog	52
		Watch entire film/TV show/theatre	49
		Evening out for meal	40
		Finish activity (eg church service, football match, bingo, hair-cut	37
		Visit family/friends	29
		Go on holiday	19
		Use public transport	16
		To queue without having to leave to go to the loo	2
D)	Psychological	To stop toilet mapping	75
		Reduce anxiety/embarrassment	21
		Feel in control	18
		Feel normal/confident	15
		To not smell	8
		To not plan life around bladder	6
		To enjoy what I am doing	3
E)	Work	Not leave meetings to go to loo	14
		To not keep leaving desk	7
		Complete an operating list	1
		To be more effective in role	1
F)	Sex	To have sex without needing the loo	2

TABLE 4 Achievement of goals

Level of achievement	% of subjects

Achieved	32.5
Exceed ed/greatly exceeded expectation	16.8
Did not achieve	18.7
Somewhat achieved	32

4 | DISCUSSION

The most common themes identified included:

4.1 | OAB

In recent literature, urgency has been described as the cardinal symptomof OAB[15] and it is the only essentialsymptom when making the diagnosis.[16] In a study by Coyne et al.,[17] the e xperience of urinary urgency had a significant negative effect on HRQL and increased symptom bother more than incontinence, frequency or nocturia. However, in this cohort of patients, the most commonly reported goal, listed by 47% of subjects was in relation to reducing nocturia episodes and only 31% of subjects listed reducing urgency as a treatment goal. This could suggest that in this group of patients, nocturia was their most bothersome symptom. It has been shown that the number of nocturia episodes per night is significantly associated with a reduction number of hours of sleep per night, reduction in QoL and sleep quality.[18] Nocturia may lead to sleep insufficiency and consequently to a decrease in mental and physical health.[19] For this cohort of patients, it is suggested that the impact of nocturia caused the largest disruption to their daily functioning perhaps as a result of sleep deprivation. However, it has also been reported that symptom bother does not always correlate with prevalence and the most commonly reported symptoms may not be the most bothersome[20]; therefore, further investigation into this group is necessary to clarify.

Although 132 subjects reported incontinence, only 86 (65%) of those added reducing incontinence episodes as a goaland only half of those reported wanting to no longer wear pads to manage their incontinence. This is a surprise as incontinence is often described as a major cause of impaired quality of life and a driver for patients to seek help. In a study by Anger et al.,[21] women with severe OAB attended focus groups and discussed their symptoms and treatment options. One of the themes that emerged was that incontinence pads were the only management strategy that provided the women with the freedom to participate in and complete activities without the worry of leakage which would result in the need to change clothes etc. Anxiety is often linked with OAB symptoms and it may be that for many of the OAB wet patients wearing pads can help reduce anxiety as it is commonly adopted as a coping strategy containing the problem. Pad use can also be a security measure or a learnt behaviour so people continue to wear pads even if their incontinence has resolved. This study did not record if patients had reduced the size of the pads that they wear or the number used throughout the day but this could be an interesting area of investigation.

It is also interesting to note that 47 patients wanted to reduce pain associated with their symptoms. Hanno et al.[22] explored the relationship between bladder pain syndrome and whether the sensation of urgency can overlap with the symptom of pain. They suggested that it is likely urgency experienced by these patients is different to that described by patients with OAB and in this cohort of patients their description of wanting to reduce pain could be in relation to pressure symptoms causing discomfort.

4.2 | Other LUTS

Under this theme, four of the sub-themes were all in relation to reduction of leakage during different activities, for example, coughing, exercising and during housework. This type of leakage is generally associated with stress incontinence but can also be attributed to provoked detrusor contractions. In this study, patients recruited reported OAB symptoms but patients with urgency predominant mixed symptoms were also included. There were no urodynamics performed to demonstrate the presence of detrusor overactivity or urodynamic stress incontinence. Therefore, it is not possible to differentiate between these groups in this analysis as to aetiology of the urinary leakage. In reality, it is unlikely that all these episodes of leakage are caused by an involuntary detrusor contraction and, therefore, these are not realistic goals for patients in this clinical trial. It could be suggested that when these goals were discussed with the clinician, a further conversation may have been warranted to clarify if these symptoms were clinically more stress related and if so patients should have been advised why it is unrealistic to e xpect symptom resolution from the therapy they received. Additionally, a discussion about alternative treatments that they could be offered for these symptoms could then be undertaken. It could also be construed as unrealistic for patients to list 'to empty bladder completely' as a goal in this study. It is an accepted side effect of fesoterodine that approximately 7% of patients will experience the symptomof incomplete bladder emptying whilst taking the medication. During the screening phase, all subjects underwent assessment of post-void residual and anyone with a significant residual volume was excluded from the trial, therefore , bladder emptying should not have been a problem for this group of patients. It could, however, be considered by some patients that they were not emptying their bladder completely as a surrogate measure of bladder irritability, if for example, the patient felt that they needed to void 10 min after having just emptied their bladder. However, this would usually result from their OAB causing after contractions and possibly poor fluid habits rather than the bladder not emptying completely.

4.3 | Finishing the task in hand

This theme highlights the frustrations in daily life that many patients with OAB suffer. The patients having to interrupt what they are doing in terms of t ravel, social life, and every day chores are common goals that patients aspire to achieve

fro mtherapy. A third of allthe patient goals in this study were in relation to being able to complete everyday tasks without having to worry about their bladder. This disruption of daily life has also been reported in a study by Irwin et al.[23] who found that 76% of individuals reporting OAB symptoms stated that the condition interfered with or made it more difficu lt to perform daily activities. Most clinic ians treating OAB patients treat the symptoms. However, for the patients, it is not always the symptoms they specifically want to change but the impact of the symptoms on their daily life. For many subjects, completing a simple tasksuch as taking the dog for a walk without needing the toilet or being able to watch a film without interruptions is what they would like to achieve from therapy. Interestingly, the SAGA tool captured these issues and should allow more focused treatment based on these concerns. Therefore, it is important to remember these motivations when planning treatment and providing bladder retrain ing, etc. as individualised management to work towards allowing the patient to complete tasks most important to the patient which will ult imately improve satisfaction and fulfill expectations.

4 | Psychological

It has been reported that patients with OAB e xperience higher rates of depressive symptoms.[23,24] In a series of interviews with patients with OAB symptoms, interviewees e xpressed constant anxiety and worry about finding and reaching a toilet in time to prevent urine leakage and some reported anxiety that constantly needing to go to the toilet created feelings of hopelessness and depression.[25] Those feelings of anxiety were mirrored in this analysis with many subjects wanting to reduce the an xiety in relation to their bladder, to stop worry ing about finding a toilet and just to feel more in control of their bladder and consequently their lives.

A recent systematic review by Sakakibara et al.[26] assessed the literature relating to bladder dysfunction in patients with anxiety and depression. They found that depression/anxiety was an obvious risk factor for OAB and presumed that this reflected that the bladder is under emotional control. They suggested that ameliorating bladder dysfunction is an important target in treating patients with depression/anxiety. However, equally these psychological symptoms could lead to anxiety and depression due to the impact of OAB on the patient's life. This study did not assess the numbers of patients suffering anxiety and depression and whether their bladder symptoms caused the anxiety and depression or conversely whether their anxiety and depression caused their bladder dysfunction.

5 | Work

This theme is similar to those set out in the finishing the task at hand theme but the impact of bladder symptoms on work productivity has been studied. According to Irwin et al.,[23] men are more likely than women to worry about the impact that OAB can have on their work life including worrying about interruption of meetings which was identified as an issue by subjects in this cohort. Also this can be a major factor in deciding the type of work or timing of retirement.

6 | Sex

There have been many studies that show the negative impact of OAB on se xual function.[27,28] These papers suggest many different reasons for this effect including embarrassment, fear of coital incontinence on penetration and orgasm, loss of confidence, fear of smelling, loss of libido. However, only two subjects reported goals in relation to sexual function in this study. It has also been suggested that concerns about time restraints, lack of effective treatments and embarrassment may prevent women in itiat ing a discussion about sexual concerns with their doctors.[29] According to O'Donnell et al.,[30] only 24% of women are not at all embarrassed to discuss sexual problems with a doctor in comparison to 87% when discussing allergies or cold/flu, and appro ximately, a third of women would not initiate a discussion about sexual issues with their doctors.[31] The very small number in this sub group could suggest that the clin ician reviewing the goals with the patient did not broach the subject of sexual function with the subjects at the time of screening and goalsetting and as the literature would imply that patients will rarely disclose this information without prompting.

In total, approximately, half of the patients in this trial achieved their goals following 12 weeks of therapy, with a further third somewhat achieving their goals.

7 | Limitations

There are several limitations to this study. Firstly, not all patients orig inally enro lled in the tria lcompleted the study so complete data are not available for all participants. It is recommended that the SA GA questionnaire is completed by thepatientwith theclinic ian. Given thatthere were 39 different sites recruiting subjects forthis study,there may bevariation in thelevelof involvementof theclin ician at eachsite andthis can introduce a risk of bias in the goals set. In areas where clinic ian involvement was minima l, this couldaccount forso mepatients setting unrealistic goals and ultimately negatively affect goal achievement. Finally, there was only a single personanalysing and categorising the open-ended goals and this may also introduce a bias in the coding system.

8 | Recommendations

This study shows the use of the SAGA questionnaire as a clin ical tool to understand how to tailor and individualise therapy to meet patient's goals and wishes.

5 | CONCLUSIONS

The analysis of these patient goals has highlighted how for many patients, their treatment aims are more focused on completion of tasks rather than a specific reduction in a particular symptom. This emphasized the impact that symptoms can have, and disruption that they can cause to their everyday activities.

The use of a more qualitative approach can help to tailor patient care based on perceived individual need and enable clinicians to support patients to develop realistic treatment goals. This may improve patient—clinician interactions and ultimately improve treatment outcomes. However, it is important to ensure that clinicians discuss all areas of treatment outcomes including sexual function.

POTENTIAL CONFLICTS OF INTEREST

Rantell—Speaker fees from Allergan, Astellas, B Braun, Mediplus, Pfizer, Uroplasty. Cardozo—During the last year received funding for research, lecturing and/or advice/ consultancies from Allergan, AMS, Astellas & Pfizer. Khullar—Consultant/speaker for Allergan, Astellas and Pfizer, research grant from Pfizer.

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How Does Lower Urinary Tract Dysfunction Affect Sexual Function in Men and Women? ICI-RS 2015 Part 1

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Aim: The aim of this paper is to review the literature on the effect of lower urinary tract symptoms (LUTS) on sexual function and dysfunction. Methods: At the International Consultation on Incontinence-Research Society (ICI-RS) in 2015, a multidisciplinary group presented a literature search of what is known about the effect of lower urinary tract dysfunction (LUTD) on sexual function (SF) in men and women. Wider discussions regarding knowledge gaps and ideal research methodology ensued. Results: A body of evidence supports associations between LUTS/urinary incontinence on SF in both men and women, but the true prevalence of the impact of LUTD on SF remains largely unknown. There is still reluctance among health care professionals (HCP's) to discuss SF with patients and often patients who are not asked will not volunteer their problems. Conclusion: A significant knowledge gap in this area remains. Education among HCP's on assessment and treatment of sexual dysfunction and communication skills are essential to encourage, and engage patients with HCP's. *Neurourol. Urodynam. 36:949–952, 2017.* # 2017 Wiley Periodicals, Inc.

Key words: future research; ICI-RS; lower urinary tract symptoms; sexual function

INTRODUCTION

Lower urinary tract symptoms (LUTS) are the subjective indicator of a disease or change in condition as perceived by the patient, carer or partner, and may lead him/her to seek help from health care professionals.[1] In 2012, the 5th International Consultation on Incontinence estimated that, of the world's population, 46% of the adults (≥20 years) experience LUTS, 11.8% complain of symptoms of an overactive bladder (OAB), 8% suffer from some type of urinary incontinence (UI), and 4% are estimated to have severe stress urinary incontinence (SUI).[2] UI is associated with reduced quality of life, higher rates of depression, reduced work productivity, and decreased enjoyment of sexual activity.[3]

In 2015, at the International Consultation on Incontinence-Research Society (ICI-RS) a multidisciplinary group of health care professionals took part in a think tank questioning how LUTS affect sexual function (SF) in men and women. This is the first of two papers developed from the literature searches performed by the clinicians involved that were presented in the think tanks and the ensuing discussions. Literature searches were performed on both Pubmed and Medline. The aim of this paper is to appraise the available evidence on the etiology and epidemiology of the effect of LUTS on sexual function and dysfunction in addition to considering the communication issues experienced by health care professionals concerning their patients' sexual function problems. The second paper will suggest proposals for further research to answer the comprehensive questions, that are still not understood. Factors common to men and women will initially be discussed before focusing on men and women separately.

Sexual Function and Dysfunction

It has been reported that, sexual behavior and relationships are key components of well-being and are affected by social norms, attitudes, and health.[4] Sexual health is a state of physical, emotional, mental, and social well-being in relation to sexuality; it is not merely the absence of disease, dysfunction,

orinfirmity .[5]Sexuallifesty les and prac tices hav e signific antly changed over the last 30 years as demonstrated by three National Surv eys of Sexual Attitudes an d Lifesty les.[1] Sexual frequ en cy and the ran ge of practices reported reduce with age , espec ially in women. However, certain sexual behaviors and lifestyle s have become increasingly more common, for e xa m- ple,sexualexperiencewith same sexpartner, and hav ing anal sex (See Table I). It was no ted thateduc ation is more s trongly ass ociate d with sexual behaviors and attitudes than socioeco- nomic status.

Acc ording to the Wo rld Health O rganization International Classifications of Diseases-10 (ICD-10), the definition of fema le sexualdy sfunction (FS D) inc ludes ''the various way s in which anin div idualisun able top artic ipatein asexualrelationship as she would wish.''[6]The re are four major cate gories of dysfu nc- tion, that is desire, arousal, orgas mic , and sexual pain disorders.[7] One in 10 women may suffer from hypoactive sexualdesire diso rder, while the rates of o rgas mic proble ms range between 3.5% and 35 %.[8] Erectile dysfunction (E D) (the persistent inability to attain and maintain an erection sufficient to permit satisfac tory sexual performance[9]) and premature ejaculation are the two main categories ofmale

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Angie Rantell and Apostolos Apostolidis have equally contributed to the manu s cr i pt, and shoul d be consi d er ed as joint first auth or s.
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TABLE I. Change in Sexual Practices Over the Past 30 Years

	1990		2010	
Sexual behavior	W omen	Men	W omen	Men
No. of partners over lifetime	3.7	8.6	7.7	12.6
No. of occasions of SA in past month	6.1	6.4	4.8	4.9
V aginal sex in the past month	76.3%	72.1%	69.6%	68%
Given or received oral sex in past month	65.6%	69.7%	75.1%	77.1%
Anal sex in past year	6.5%	7%	15.1%	17%
S exual experience with same sex partner	3.7%	6%	16%	7.3%
M asturbated inpast 4/52	n/a	n/a	32.9%	66.4%

SA, sexual activity.

sexual dysfunction.[10] A high prevalence and incidence of ED has been shown by epide mio logical data worldwide. The Massachusetts Male Aging Study (MMAS)[11] reported an overall prevalence of 52% in non-institution alized men aged 40 –70 years (Boston area); among these men, 17.2%, 25.2%, and 9.6%, respectively suffered from minimal, moderate, and complete ED. In the Cologne study of men aged 30 –80 years,the overall prevalence ofEDwas 19 .2%, with a steep age-related inc rease from 2.3% to 53.4 %.[12] There are de monstrable differenc es between the sexes when assessing the type of sexual dysfunction as reported by the work of Richters et al.[13] set out in Table II.

There is evidence to show that FSD related to UI c an also adversely impact upon relationships as men with partners with UI reported an overall dimin ished sexual function, lower freq uency of intercourse, reduced satisfaction, and were more likely to have erectile problems.[14]

Let s Talk About Sex!

Communication betweenhealth care professionals (HCPs) and patients about sexual function, and Lower urinary trac t dysfunction (LUTD) has long been an issue. Patients will seldom volunteer sexual proble ms but HC P's enquiring is often met with reliefratherth ane mbarrass ment.[15]However,in a recent study of Ame rican obstetricians and gynaecologists, 63% ask if the patient is sexually activ e but only 40% routinely enquire about sexualp roble ms .[16]Yet it has beenshown th at patients are more likely to seekhelp if a HCP has as kedthe m about SF during a routine v isit in the p rev ious 3 years.[17] In addition , when communicating sexual proble ms there are variations betweenthesexesas menpreferto discussSFwith aphysic ian and women prefer to discuss it with a nurse.[18] A systematic

TABLE II. Differences in Types of Dysfunction Between the Sexes

Type of dysfun ction	Men (%)	Women (%)
Lack of interest	25	55
Coming to orgasm too quickly	24	12
Inability to come to orgasm	6	29
Not finding sex pleasurable	6	29
Pain during intercourse	2	20
W orry over how body looks	2	20

Box 1 Themes Identified

- open up ac anofworms''
- Lack oftime/resources/training
- Concern about knowledge and ability
- Worry will cause offense
- Personal discomfort
- Lack of awareness about sexual issues
- Opposite gender/race/age concerns

review of qualitative research in the UK revealed many

Anxiety about performance	16	17
V aginal dryness	—	24
Trouble maintaining erection	10	—

comm o n the me s why HCP' s do not talk about sex[19] (See Box 1).

How Does LUTD Affect Sexual Function in Men?

Multifactorial aetiology of male sexual dy sfunction. From a physiological perspective pelvic organ functions cannot be regarded separately as there are countless interac tions in the neuronal network of the pelv is that inv olves bladder, bowel, and sexual functions. Furthermore, vascular, hormo nal, cellu- lar, and other fac tors comprehensively affec t pelvic organ functions.LUTS and ED in males share commonpathophysio- logical pathway s.[20–22] An overview of the extensive relation- ship between ED and LUTS in men with e mphasis on phosphodie sterase-5 function has been summarized in Fig ure 1 by *Koehler and McVary*.[23]

Effects of LUTS/incontinence on male sexual function—epidem iological data. Large population -based studies have extensively documented increased sexual dysfunctio n (SD) in men with storage and voiding LUTS. Records from 11,327 men inUK general practices using the Health Improve ment Network database showed an increase in the overall prevalence of recorded SD from 1.7% in 2000 to 4.9% in 2007.[24] The odds ratio (OR) for ED was 3.0 (2.6–3.4) for storage LUTS, 2.6 (2.4–2.7) for voiding LUTS,and 4 .0 (3 .4–4 .8) fo rvoiding an dsto rage LUTS, respectiv ely . Likewise, the EpiLUTS study , a c ross-sec tional, po pulation-re pre se ntative survey via inte rnet con ducte d in the UK,Sweden,and USAwith 6 ,326 men inv olved,de monstrated an impact of OAB on sexual health.[25] Both O AB wet and O AB dry were assoc iated with worse sexualhealth,reducedsexual ac tiv ity , and diminished enjoyment of sex ($P < 0.0001$). OAB dry/wet were significant predictors of ED and ejac ulatory dysfunction(EjD) in men. According to a large study by Rosen etal., the presenc e and severity ofLUTS are independentrisk factors for sexua l dysfu n ctio n in olde r men. [26]

How Does LUTD Affect Sexual Function in Women?

Multifactorial aetiology of female sexual dysfunction. Further to the well studied psychological and relationship aspects, a variety of mostly organic factors may be inv olved in the pathophysiology of FSD. Endocrine, neurological, cardi ovascu- lar, dermatolog ic al, and psychiatric disorders, as well as surgic al and medical complic ations, and c ancer may lead to central and pe ripheral changes in cell-to-cell co mmunication, changes in endocrine milieu, disruption in the homeostasis of neurotransmitters and signal mole cules, tiss ue da mage, organ damage, vas cular, and ne urological changes which predisp ose to FSD.[27,28]

Effects of LUTS/incontinence on female sexual function—epidemiologicaldata. An inc reasing body of evidence supports an assoc iation betweenLUTDand FS D.[29–33] Thelatterappears

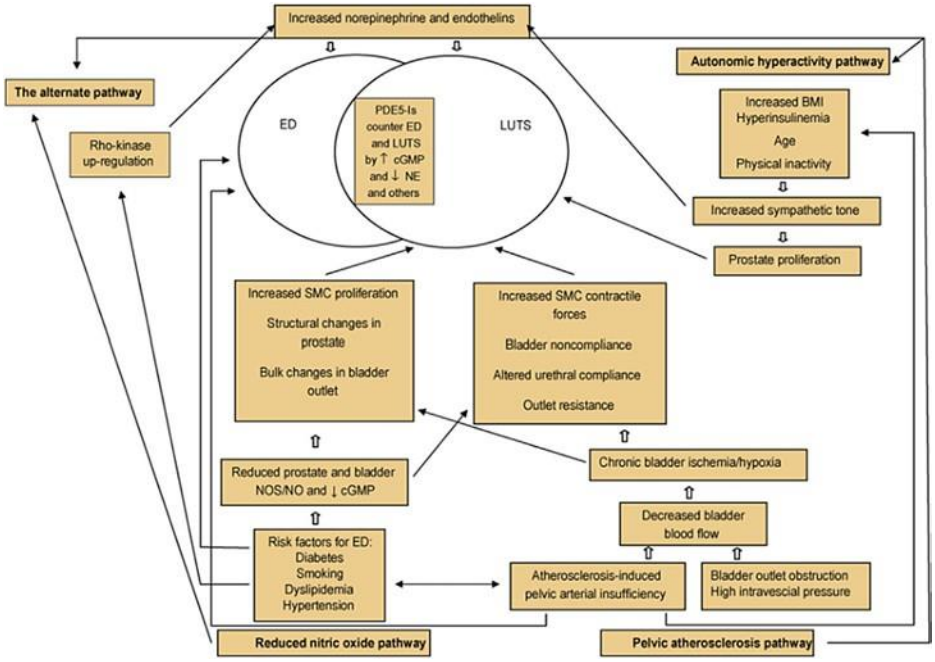

Fig. 1. Fig. 1 An overview of the extensive relationship between erectile dysfunction and lower urinary tract symptoms in men with emphasis on pho sp h o di e ste r a se - 5 functi o n has been summ a ri z e d in Fig ur e 1 by Koeh l er and McVar y .[23]

to be quite prevalentamong womenwith LUTS and/or UI. The presence of severe UI doubled the odds compared to non-incontinent women fo r reduced libido, v aginal dryness, an d dysp are u nia. [6]

Shaw (2002) undertook a systematic rev iew of c linic al papers published between 1980 and 2001 to assess the prevalence of sexual impairment in women with UI an d the prevalence of urinary leakage during sexual activ ity . Prev alence ofsexual incontinence in c linicalsettings ranged fro m 10–56% and impairment in sexual function was reported as 0.6–64%. Recommendations for standard defi- nitions and measures of sexual incontinence and sexual impairment were suggested to establish reliable prevalence estimates.[34]

All types of UI were found to be associated with FSD. Urodynamic ally proven SUI was found to correlate with a dimin ished quality oflife,inc reased ris kof marital proble ms, and reduced sexual satisfac tion,[4] but women with detrusor overactivity and associated UI had the greatest degree of sexual dysfunction. A c linic al diagnosis of O AB was also assoc iated with impairment of fe male sexual function. Women with mixed UI had the worst sexual function.[35] Concerning the effect ofUIon ind iv idualdo mains offe malesexualfunc tion,while all types of UI increased the risk for FSD by 1.6-fold to 1.8-fold, pure Urgency UI was a risk fac tor for decreased lubric ation and increasedcoitalp ain while mixed UI was assoc iated with less sexual satisfaction.[36]

OAB and sexual function—whatdo we actually know? Large epidemiolog ic al studies, such as the EpiLUTS study , c learly suggest associations between OAB and sexual dysfunctions,[37] but existing literatu re is partia lly contradic tory. In a large treatment outcomes study, only 37% of the female participants c laimed a negativ e sexual and relationship impact of OAB in theirliv es.Mo reover,in a multiv ariate analy sis,OAB was nota predictorofloss ofinterestinsex in the fe male partic ipants as opposed to the male ones and improvement of OAB symptoms was followed by asimilar improvementin sex liv es only in 19% of the patients, with another 11% even reporting a deterioration.[38] By contrast, other published studies, which used tolterodine showed beneficial effec ts of both the immediate release (IR) and extendedrelease (ER) formulations on sexual health outcomes. Sexual desire, arousal, vaginal lubrication, orgasm, and orgasm satisfaction improved for up to 6 months of treatment.[39-41]

CONCLUSION

S

Sexual practices are changing. Although a plethora of studies support associations between LUTD and sexual dysfunction in both sexes,little is known about the mechanis ms underlying the impac t of LUTS and LUTD on SF and vice versa. Some proble ms are common to both men and women but there are also differences that may be related to age, ethnicity, and cult ural background. Education among HCP's on assessment and treatment of sexual dysfunction and communication skills are essential to encourage an initial engage ment between patients and HCP's . However,this will not overcome all of the barriers identified.

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REVIE W ARTICLE

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How does lower urinary tract dysfunction (LUTD) affect sexual function in men and women? ICI-RS 2015—Part 2

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AIM : To discuss available data on the links between LUTD and se xual dysfunction, what is still unknown about the causative effect of disease processes on sexual function (SF), and to suggest proposals for further research.

METHODS: At the 2015 International Consultation on Incontinence-Research Society (ICI-RS), a multi-disciplinary group presented a literature search of what is known about the effect of LUTD on SF in men and women. Wider discussions regarding knowledge gaps, and ideal research methodology ensued and are presented.

RESULTS: The underlying mechanis ms of the impact of LUTD on SF remain largely unknown. Risk factors for the metabolic syndrome may cause both LUTS and ED in men, and their improvement may improve both conditions. In women, neurovascular changes may be common in LUTD and FSD. Successful LUTS management results in FSD improvement, but the mechanis ms are ill understood. Gaps in standardization of sexua l dysfunction terminology, variations of assessment, and treatment in clinical practice and research make most studies not comparable. The sensitive knowledge and subjective nature of the problem present challenges and often result in neglecting it.

CONCLUSION: Neurovascular and hormonal factors, but also indirect effects may lin k LUTD to SD in both sexes, but the evidence is not robust and the mechanisms unclear. There is a need for defining the terminology and standardizing outcomes assessed in clinical trials. The multifactorial nature of SF in both sexes makes trial design challenging and "real world" studies may prove more beneficial for patients' outcomes and clinicians' understanding.

KEYWORD S
animal models, erectile dysfunction, female sexual dysfunction, incontinence, lower urinary tract symptoms, metabolic syndrome, neuromodulation

1 | INTRODUCTION

Both lower urinary tract symptoms (LUTS) and sexual dysfunctions (SD) are common conditions, their prevalence increasing with advanced age and the emergence of comorbidities.[1–4] Epidemiological data but also clinical and basic research findings support links between LUTS and SD,[5–8] particularly in men where common oral treatments (phosphodiesterase type 5 inhibitors) are now available to manage both conditions simultaneously.[8,9] However, the multifactorial etiology of both LUTS and SD and the sociocultural issues surrounding them may have negatively affected treatment seeking and physician–patient

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communication. Data demonstrate increasing patients' knowledge of both conditions in the last decades; however, gaps in identifying both conditions as problems and understanding them, particularly when possible associations between them are considered, still remain (see also Part 1[10]).[11,12]

At the International Consultation on Incontinence-Research Society (ICI-RS) in 2015, a multidisciplinary group of health care professionals participated in a think tank (TT) questioning how LUT dysfunction (LUTD) affects sexual function (SF) in men and women. In the first part, the panelists appraised the available evidence on the etiology and epidemiology of the effect of LUTD on SF in addition to considering the communication issues experi- enced by health care professionals.[10] In the second part, the panel aimed to discuss literature data considering how the two conditions could be linked (thus including, possible common causes, common patients' characteristics, etc.) in men and women and put forward proposals for further research to answer the comprehensive questions that are still not understood. The search terms erectile dysfunction, female se xual dysfunction, lower urinary tract symptoms, incontinence, metabolic syndrome, neuro-modulation, animal models were used in combination for a literature search of both PubMed and Medicine, which served to set the basis for the discussion of the TT. However, the work of the TT does not represent a systematic review of the literature.

2 | ARE THERE CAUSATIVE LINKS BETWEEN LUTD AND SF IN MEN?

Unfavorable etio logical risk factors like diabetes mellitus (DM), obesity, and the metabolic syndrome promote both LUTS and ED progression. This association has beenwidely studied, a literature search (1990–2008) and a summary of 16 well-designed studies with over 50 000 subjects highlights the cause-and-effect relationship between LUTS and ED.[8] Since then, more evidence with the same conclusions has been published. A recent questionnaire-based study showed that OAB-wet increased the risk and severity of ED in men with DM type 2.[13] The OR of ED in patients with OAB-dry or OAB-wet compared with no OAB was 1.82 and 3.61, respectively. Among the OAB components, urgency urinary incontinence (UUI) had the strongest impact on ED (OR = 4.06), followed by nocturia, urgency, and frequency. These findings suggest a potential influence of urinary incontinence (UI) on male se xua l function in addition to the effect of LUTS. Whether this is a psychologicale ffect related to the loss of bladder controlor even to the use of pads/diapers or whether it implies a worsening of the underlying disease processes and mechanisms affecting SF is yet unclear.

The US Health Professionals Follow-up Study (HPFS) with 18 055 men involved demonstrated a significant increase in the risk of LUTS and LUTS progression with increasing BMI (≥35 kg/ m^2 vs. <25), waist circumference (≥42 inches vs. <33), and weight gain beyond 21 years of age (≥50 pounds vs. stable).[14] The Third National Health and Nutrition Examination Survey (NHANES III)[15] demonstrated the association between markers of the metabolic syndrome such as oral glucose tolerance test, glycosylated hemoglobin, HDL and LDL cholesterol, triglycerides, history of DM, hypertension, and LUTS in elderly men. Both a history of diabetes (OR 1.67) and hypertension (OR 1.76), as well as increasing glycosylated hemoglobin (P = 0.005) showed a positive association with LUTS. If more than three components of the metabolic syndrome were present, the likelihood of LUTS further increased (OR 1.80).

The same risk factors apply for hypogonadism in men, which play a key role in the development of ED. Current evidence suggests that hypogonadism itself is an important risk factor for LUTS, too.[16] In the Hypogonadism in Males (HIM) study of men over 45, the prevalence rates of hypogonadismwere 52.4% for obesity (OR 2.38), 50.0% for diabetes (OR 2.09), 42.4% for hypertension (OR 1.84), and 40.4% for hyperlipidemia (OR 1.47), the four criteria of the metabolic syndrome.[17] The more components of the metabolic syndrome are present, the higher is the prevalence of hypogonadismin men with SD.[18]

These demonstrated correlations between unhealthy liv ing and the development of LUTS and ED also offer a pathway to a therapeutic approach. The Osteoporotic Fractures in Men Study showed that obesity increases and physical activity decreases the risk for LUTS in older men (65+).[19] In multivariate analyses, compared with men of normal weight at baseline (BMI < 25 kg/ m^2), overweight (25–30 kg/m^2), and obese (≥30 kg/m^2) men were 29% (OR 1.29) and 41% (OR 1.41) more likely to develop LUTS, respectively. Men in the highest quartile of physical activity were 29% (OR 0.71) and those who walked daily 20% (OR 0.80) less likely than their sedentary peers to develop LUTS, adjusting for BMI. *Patel & Parsons* separated non-modifiable risk factors (age, genetics, geography) from modifiable ones (hormones, metabolic syndrome, obesity, diet, physical activity, inflammation).[20] Beside all options to reduce weight including diet and physical activity, long- term testosterone therapy in obese hypogonadal men with type 2 DM resulted in a significant and durable reduction of waist circumference and weight over a 6-year treatment period.[21] However, in a study of Tamsulosin monotherapy versus combination therapy with Tamsulosin and solifena- cin improvements in voiding, storage symptoms and Qo L were not followed by erectile function improvements.[22]

Further to the established associations between LUTS and ED in several disease processes, the question whether

male LUTD can affect se xual function cannot be answered yet although mechanisms linking LUTS to ED have been proposed based on a wealth of preclinical and clinical evidence. *Kohler and McVary*[8] put forward a 4-theory complex where altered nitric oxide (NO) levels/cyclic guanosine monophosphate (cGMP) pathway, autonomic hyperactivity (AH), increased Rho-kinase activation, and/or pelvic atherosclerosis may contribute to the development of both LUTS and ED. In vitro e xpe riments with NO donors showed a dose-dependent accumulation of c GMP and a time-dependent reduction in the growth of human prostate smooth muscle cells.[23] The autonomic nervous system is thought to be associated with prostate growth and function,[24] while patients with AH have increased risk for developing LUTS, and α1-adrenoreceptors in the spinal cord and peripheral ganglia have been linked with spinal hypersensitivity to stimuli, bladder overactivity, and ejaculatory control.[8] Increased Rho-kinase activation induces smooth muscle contraction, but also inhibits activation of eNOS in human endothelium. In addition, dysfunction of the Rho-pathway has been identified in the bladder following BOO.[8] Pelvic atherosclerosis/ischemia is associated with the metabolic syndrome and AH, leads to enhancement of Rho-kinase activation, and reduces the e xpression of NOS. In this respect, similar histopathologic changes were noted in smooth muscle of the bladder, prostate, and penis of animal models of hypercholesterol- emia and pelvic ischemia.[8]

Besides common pathophysiological mechanis ms, research findings suggest causative associations between BPH and ED. Electrophysiologicalhuman studies show that nerves of the prostatic capsule contribute to erectile function and their triggering increases intracavernous pressure.[25] BOO was found to enhance the tone of the corpora cavernosal smooth muscle via an increase of Rho-kinase expression in the cavernosal tissue.[26] In animal models, partial BOO resulted in morphological and innervation changes of the corpus cavernosum smooth muscle leading to impaired relaxation.[27]

3 | EFFECT OF SURGERY-ASSOCIATED INCONTINENCE

A long-neglected problem is the impact of post-prostatectomy incontinence (PPI) on SF with limited data available[28–32] as most studies focus on sexual dysfunction as direct consequence of surgery. In a questionnaire based study, orgasm-associated incontinence after radical prostatectomy was reported by 93% of the 239 respondents.[28] Orgasm-associated urine leakage occurred always in 16%, occasionally in 44%, rarely in 33%, and never in 7%. This condition was later called "climacturia,"[29] with 42% of patients reporting loss of at least an ounce of urine each time and 47% considering it a significant bother to their quality of life. No differences were seen in prevalence between open and robot-assisted radical prostatectomy (RARP), but recovery fro m climacturia was faster and greater after RARP (48% vs. 15% at 84 months).[30] In a small series, 7/11 (64%) patients reported the impact of PPI as a major problem during arousaland 4/11 (36%) as a major problem at the time of orgasm.[33] After successful surgical management of PPI, 7/11 (64%) patients reported a marked improvement of their sexual quality of life.

4 | WHAT WE DO NOT KNOW—SUGGESTIONS FOR RESEARCH

Standard LUTS therapy in men with BPE might even deteriorate erectile and/or ejaculatory function. Several drugs like alpha-bloc kers and 5-alpha reductase inhibitors can be associated with bothersome sexual side effects.[34] On the other hand, evidence in the recent years suggests that ED treatment with phosphodiesterase type 5 (PDE5) inhibitors can also improve LUTS.[35,36] Such effects may be associated with a reduction in the growth rate of prostatic stromal cells (human) or of the contractile act ivity of prostatic and urethra l smooth muscle, in addition to a decrease of uninhibited detrusor contractions (animals).[37] This gives reason for a combination treatment in men with LUTS and ED that can improve both conditions.[38–40] In vitro human studies demonstrated an additive rela xant effect of tadalafil and alfu zosin on both the prostate and the bladder.[41] Furthermore, therapeutic modalities like sacral neuromodulation already established in the treatment of refractory UUI are being investigated for possible beneficialeffects in patients with ED and show promising results.[42] These approaches give plenty of room for future research, both in pharmacological and clinical respects.

5 | ARE THERE CAUSATIVE LINKS BETWEEN LUTD AND SF IN WOMEN?

Improvements in women's SF fo llo wing successful treatment of either OAB/UI or stress UI suggest indirect effects of LUTD on SF. Improvement of secondary parameters as a result of OAB/UI (leakage during intercourse, intercourse interruption due to urgency, pain during intercourse) and of factors which have a negative effect on the satisfaction of the sexual relationships as well as on patients' self-image (embarrassment associated with OAB/UI, fear of leakage during stimulation and intercourse, post-coital worsening of

OAB) may also result in improvement of FSD.[43,44] In the case of stress UI, surgical or conservative restoration of continence is commonly associated with improvement of SF as demonstrated by most prospective studies,[45–49] literature reviews,[50] and meta-analyses.[51] The cure of coital incontinence, achieved in 90% of surgically treated cases, is thought to be a major predictor of sexual improvement,[46,47,50] with improvements in coital pain[47] and in partner-related aspects[48,52] also reported to be associated with post-surgery SF beneficial effects.

The use of neuromodulation to treat refractory LUTD could shed some light in the mechanisms connecting LUTD to FSD. Almost all studies showthat sacralneuromodulation (SNM) improves LUTS and SF irrespective of the cause of LUTD.[53–56] Their findings suggest that neuraland vascular changes may be common in LUTD and FSD. In this respect, women with refractory OAB and non-obstructive urinary retention were found to have abnormal pudendal nerve function, which showed a trend towards improvement after SNM.[57] Neurally augmented sexual function was achieved by percutaneous epidural spinal cord space stimulation, resulting in reproducible pleasurable genital stimulation, increased frequency of sexual activity and lubrication, and improved orgasmic function.[58] Active neurostimulation could also increase the vaginal pulse amplitude with both erotic and non-erotic stimuli.[59] Whether neurovascular changes proposed in the 4-theory complex to explain associations between male LUTS and ED also apply for LUTD and female sexual dysfunction needs be further researched.[8]

6 | ARE CHANGES IN SELF- IMAGE/ BODY IMAGE CONNECTED TO SD AND LUTS IN WOMEN?

Body image problems are known to be associated with greater sexual problems. There are sparse data on correlations between self-image and SD in women with LUTS. Sexual function was found to be affected by body image perception in women with pelvic organ prolapse.[60] In neurological conditions, the presence of an indwelling catheter had a negative impact on female sexuality and quality of life (QoL). Urinary tract reconstruction restored QoL and markedly improved SF by improving self-image, self-esteem, and the ability to cope.[61] In women undergoing surgery for stress UI, the goals of improving sexuality and body image are predictors of post-treatment SF improvement,[62] but there is still no available literature on the impact of urgency or mixed UI on patients' self-image, and its possible associations with SF. The impact of using pads and diapers on patients' self-image and SF has not been studied either.

7 | WHAT WE DO NOT KNOW— SUGGESTIONS FOR RESEARCH

Data concerning the (patho) physiology of female SF have largely been obtained from animal studies. Animal models used for the study of female sexual behavior and function include anesthetized models of nerve stimulation, chemically induced responses and electrical stimulation of the central nervous system, reproductive behavior models, and urogenital reflex models for the study of orgasm.[63] However, despite the use of a variety of models for the study of either FSD or LUTD, the two conditions have not been studied in a single model. In addition, the translational value of these models is unknown, as medical treatments of SD have mostly been evaluated in male models. Finally, it is questionable if animal models could reproduce all or most parameters involved in the multifactorial pathophysiology of human FSD.

Nevertheless, an increasing amount of novel evidence also comes from human studies. Researchers in the field have previously identified axes for further research: (i) sexual differentiation of the brain, as it affects behavioral sex differentiation; (ii) central neurobiology of sexual function, using neuroimaging methods during arousaland orgasm; (iii) peripheral functional anatomy, in order to address genital arousal and orgasm aspects; (iv) interactions between physiological and psychological states of women's sexual response. In addition, more specific clinical aspects, such as associations between OAB/UI and SD, the effect of OAB/UI treatment on SF, associations between self-image/body image and SD in women with LUTS/ UI could be further investigated in order to approach a more holistic patient management.

8 | COMMUNICATION

The overriding discussion in the ICI-RS 2015 session was in relation to communication and understanding what patients actually want. This is not only in the context of how to approach the topic and talk about sexual behaviors but to gauge how many men and women actually see sexual dysfunction as a problem and have the desire for treatment. In order to encourage good quality trials in the area, it is felt necessary to develop standardized terminology for sexual dysfunction as well as setting recommendations for outcomes measures to be used so that comparisons can be made. The education or lack thereof for all HCP's on SF and LUTS was raised as an issue that needs to be addressed in clinical practice to enable appropriate care to be received by patients who raise concerns and express a desire for treatment but also so that HCP's do not ignore the issue because they do not know how to handle the information the patient has given. Research priorities and the knowledge gaps identified to start

TABLE 1 Proposal for further research concerning the associations between LUTD and sexual dysfunction in men and women

1. Research priorities	• Development of standardized terminology for sexual dysfunction in men and women
	• Routine use of standardized outcome measures in clinical trials
	• Qualitative study to understand what patients want in relation to discussion, assessment, and treatment (or not) of LUTS and sexual dysfunction
2. Epidemiology	• What is the true prevalence of the problem? Focus should be on patients' perspectives and wishes in a changing world with respect to gender, age, and cultural environment
3. Basic science	• Are there reliable animal models to study the multifactorial pathophysiology of human FSD?
	• Can the 4-theory complex of interrelations between LUTS and sexual dysfunction be explored in animal models and human studies in both sexes?
4. Clinical	• What are the psychological impacts/ bothersomeness for the patient and for their partner?
	• How does treatment of LUTD affect sexual function in men and women?
5. Research challenges	• How can we control for external factors/ compounding variables that also affect SF, e.g., relationship issues?
	• How do patients want to be approached and questioned about SF?

to gain a deeper understanding in this area are listed below (Table 1).

9 | CONCLUSIONS

There is a lack of evidence available to accurately define how LUTD/LUTS affect SF in men and women. Neurovascular and hormonal factors, but also indirect effects may be linking LUTD to SD in both sexes, but the substantiation is still not robust and the mechanisms unclear. The main areas of research have been identified to provide better assessment and more appropriately targeted management. There is a need for defining the terminology and standardizing outcomes assessed in clinical trials. The multifactorial nature of SF in men and women makes trial design challenging and "real world" studies may prove more beneficial for patients' outcomes and clinicians' understanding.

10 | POTENTIAL CONFLICTS OF INTEREST

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Before you contact this company: often several companies will market medicines with the same active ingredient. Please check that this is the correct company before contacting them. **Why?**

Summary of Product Characteristics last updated on the eMC: 04/04/2011

TOVIAZ 4 mg prolonged-release tablets & TOVIAZ 8 mg prolonged-release tablets

▼ This medicine is monitored intensively by the CHM and MHRA

1. NAME OF THE MEDICINAL PRODUCT

TOVIAZ ▼ 4 mg prolonged-release tablets

TOVIAZ ▼ 8 mg prolonged-release tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 4mg prolonged-release tablet contains fesoterodine fumarate 4 mg corresponding to 3.1 mg of fesoterodine. Each 8mg prolonged-release tablet contains fesoterodine fumarate 8 mg corresponding to 6.2 mg of fesoterodine.

Excipients

Each 4 mg prolonged-release tablet contains 0.525 mg of soya lecithin and 91.125 mg lactose monohydrate. Each 8 mg prolonged-release tablet contains 0.525 mg of soya lecithin and 58.125 mg lactose monohydrate. For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Prolonged-release tablets

The 4 mg tablets are light blue, oval, biconvex, film-coated, and engraved on one side with the letters 'FS'.

The 8 mg tablets are blue, oval, biconvex, film-coated, and engraved on one side with the letters 'FT'.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of the symptoms (increased urinary frequency and/or urgency and/or urgency incontinence) that may occur in patients with overactive bladder syndrome.

4.2 Posology and method of administration

Adults (including elderly)

The recommended starting dose is 4 mg once daily. Based upon individual response, the dose may be increased to 8 mg once daily. The maximum daily dose is 8 mg.

Full treatment effect was observed between 2 and 8 weeks. Hence, it is recommended to re-evaluate the efficacy for the individual patient after 8 weeks of treatment.

Tablets are to be taken once daily with liquid and swallowed whole. TOVIAZ can be administered with or without food.

In subjects with normal renal and hepatic function receiving concomitant administration of potent CYP3A4 inhibitors, the maximum daily dose of TOVIAZ should be 4 mg once daily (see section 4.5).

Renal and hepatic impairment

The following table provides the daily dosing recommendations for subjects with renal or hepatic impairment in the absence and presence of moderate and potent CYP3A4 inhibitors (see sections 4.3, 4.4, 4.5 and 5.2).

		Moderate[3] or potent[4] CYP3A4 inhibitors		
		None	Moderate	Potent
Renal impairment[1]	Mild	4 → 8 mg[2]	4 mg	Should be avoided
	Moderate	4 → 8 mg[2]	4 mg	Contraindicated
	Severe	4 mg	Should be avoided	Contraindicated
Hepatic impairment	Mild	4 → 8 mg[2]	4 mg	Should be avoided
	Moderate	4 mg	Should be avoided	Contraindicated

(1) Mild GFR = 50-80 ml/min; Moderate GFR = 30-50 ml/min; Severe GFR = <30 ml/min

(2) Cautious dose increase. See sections 4.4, 4.5 and 5.2

(3) Moderate CYP3A4 inhibitors. See section 4.5

(4) Potent CYP3A4 inhibitors. See sections 4.3, 4.4 and 4.5

TOVIAZ is contraindicated in subjects with severe hepatic impairment (see section

4.3). Paediatric population

TOVIAZ is not recommended for use in children and adolescents below 18 years of age due to lack of data on safety and efficacy (see section 5.2).

4.3 Contraindications

- Hypersensitivity to the active substance or to peanut or soya or any of the excipients
- Urinary retention
- Gastric retention
- Uncontrolled narrow angle glaucoma
- Myasthenia gravis
- Severe hepatic impairment (Child Pugh C)
- Concomitant use of potent CYP3A4 inhibitors in subjects with moderate to severe hepatic or renal impairment
- Severe ulcerative colitis
- Toxic megacolon.

4.4 Special warnings and precautions for use

TOVIAZ should be used with caution in patients with:

- Clinically significant bladder outflow obstruction at risk of urinary retention (e.g. clinically significant prostate enlargement due to benign prostatic hyperplasia, see section 4.3)

- Gastrointestinal obstructive disorders (e.g. pyloric stenosis)

- Gastro-oesophageal reflux and/or who are concurrently taking medicinal products (such as oral bisphosphonates) that can cause or exacerbate oesophagitis

- Decreased gastrointestinal motility

- Autonomic neuropathy

- Controlled narrow-angle glaucoma

Caution should be exercised when prescribing or uptitrating fesoterodine to patients in whom an increased exposure to the active metabolite (see section 5.1) is expected:

- Hepatic impairment (see sections 4.2, 4.3 and 5.2)

- Renal impairment (see section 4.2, 4.3 and 5.2)

- Concomitant administration of potent or moderate CYP3A4 inhibitors (see sections 4.2 and 4.5)

- Concomitant administration of a potent CYP2D6 inhibitor (see sections 4.5 and 5.2).

In patients with a combination of these factors, additional exposure increases are expected. Dose dependent antimuscarinic side effects are likely to occur. In populations where the dose may be increased to 8 mg once daily, the dose increase should be preceded by an evaluation of the individual response and tolerability.

As with all medicinal products indicated for the treatment of overactive bladder, organic causes must be excluded before any treatment with antimuscarinics is considered. Safety and efficacy have not yet been established in patients with a neurogenic cause for detrusor overactivity.

Other causes of frequent urination (treatment of heart failure or renal disease) should be assessed before treatment with fesoterodine. If urinary tract infection is present, an appropriate medical approach should be taken/antibacterial therapy should be started.

The concomitant use of fesoterodine with a potent CYP3A4 inducer (i.e. carbamazepine, rifampicin, phenobarbital, phenytoin, St John's Wort) is not recommended (see section 4.5).

As with other antimuscarinics, fesoterodine should be used with caution in patients with risk for QT-prolongation (e.g. hypokalaemia, bradycardia and concomitant administration of medicines known to prolong QT interval) and relevant pre-existing cardiac diseases (e.g. myocardial ischaemia, arrhythmia, congestive heart failure), (see section 4.8). This especially holds true when taking potent CYP3A4 inhibitors (see sections 4.2, 4.5 and 5.1).

Lactose

TOVIAZ prolonged-release tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacological interactions

Caution should be exercised in coadministration of fesoterodine with other antimuscarinic agents and medicinal products with anticholinergic properties (e.g. amantadine, tri-cyclic antidepressants, certain neuroleptics) as this may lead to more pronounced therapeutic- and side-effects (e.g. constipation, dry mouth, drowsiness, urinary retention).

Fesoterodine may reduce the effect of medicinal products that stimulate the motility of the gastro-intestinal tract, such as metoclopramide.

Pharmacokinetic interactions

In vitro data demonstrate that the active metabolite of fesoterodine does not inhibit CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, or 3A4, or induce CYP1A2, 2B6, 2C9, 2C19, or 3A4 at clinically relevant plasma concentrations. Thus fesoterodine is unlikely to alter the clearance of medicinal products that are metabolised by these enzymes.

CYP3A4 Inhibitors

Potent CYP3A4 Inhibitors

Following inhibition of CYP3A4 by co-administration of ketoconazole 200 mg twice daily, C_{max} and AUC of the active metabolite of fesoterodine increased 2.0 and 2.3-fold in CYP2D6 extensive metabolisers and 2.1 and 2.5-fold in CYP2D6 poor metabolisers, respectively. Therefore, the maximum dose of fesoterodine should be restricted to 4 mg when used concomitantly with potent CYP3A4 inhibitors (e.g. atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir (and all ritonavir boosted PI-regimens), saquinovir and telithromycin (see sections 4.2 and 4.4)).

Moderate CYP3A4 Inhibitors

Following blockade of CYP3A4 by coadministration of the moderate CYP3A4 inhibitor fluconazole 200 mg twice a day for 2 days, C_{max} and AUC of the active metabolite of fesoterodine increased approximately 19% and 27%, respectively. No dosing adjustments are recommended in the presence of moderate CYP3A4 inhibitors (e.g., erythromycin, fluconazole, diltiazem, verapamil and grapefruit juice).

Weak CYP3A4 Inhibitors

The effect of weak CYP3A4 inhibitors (e.g. cimetidine), was not examined; it is not expected to be in excess of the effect of moderate inhibitor.

CYP3A4 Inducers

Following induction of CYP3A4 by coadministration of rifampicin 600 mg once a day, C_{max} and AUC of the active metabolite of fesoterodine decreased by approximately 70% and 75%, respectively, after oral administration of fesoterodine 8 mg.

Induction of CYP3A4 may lead to subtherapeutic plasma levels. Concomitant use with CYP3A4 inducers (e.g. carbamazepine, rifampicin, phenobarbital, phenytoin, St John's Wort) is not recommended (see section 4.4).

CYP2D6 Inhibitors

The interaction with CYP2D6 inhibitors was not tested clinically. Mean C_{max} and AUC of the active metabolite are 1.7 and 2-fold higher, respectively, in CYP2D6 poor metabolisers as compared to extensive metabolisers. Co-administration of a potent CYP2D6 inhibitor may result in increased exposure and adverse events. A dose reduction to 4 mg may be needed (see section 4.4).

Oral contraceptives

Fesoterodine does not impair the suppression of ovulation by oral hormonal contraception. In the presence of fesoterodine there are no changes in the plasma concentrations of combined oral contraceptives containing ethinylestradiol and levonorgestrel.

Warfarin

A clinical study in healthy volunteers has shown that fesoterodine 8 mg once daily has no significant effect on the pharmacokinetics or the anticoagulant activity of a single dose of warfarin.

4.6 Pregnancy and lactation

Pregnancy

There are no adequate data from the use of fesoterodine in pregnant women. Reproductive toxicity studies with fesoterodine in animals show minor embryotoxicity (see section 5.3). The potential risk for humans is unknown. TOVIAZ is not recommended during pregnancy.

Lactation

It is not known whether fesoterodine is excreted into human milk; therefore, breast-feeding is not recommended during treatment with TOVIAZ.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. As with other antimuscarinic agents, caution should be exercised when driving or using machines due to possible occurrence of side effects such as blurred vision, dizziness, and somnolence (see section 4.8).

4.8 Undesirable effects

The safety of fesoterodine was evaluated in placebo-controlled clinical studies in a total of 2859 patients with overactive bladder, of which 780 received placebo.

Due to the pharmacological properties of fesoterodine, treatment may cause mild to moderate antimuscarinic effects like dry mouth, dry eye, dyspepsia and constipation. Urinary retention may occur uncommonly.

Dry mouth, the only very common event, occurred with a frequency of 28.8% in the fesoterodine group compared to 8.5% in the placebo group. The majority of ADRs occurred during the first month of treatment with the exception of cases classified as urinary retention or post void residual urine greater than 200 ml, which could occur after long term treatment and was more common in male than female subjects.

The table below gives the frequency of treatment emergent adverse reactions from placebo-controlled clinical trials and from post-marketing experience. The adverse reactions reported in this table are those events that were very common (≥ 1/10), common (≥ 1/100 to <1/10), uncommon (≥ 1/1,000 to <1/100) or rare (≥ D 1/10,000 to < 1/1,000).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

System Organ Class	Very common	Common	Uncommon	Rare
Cardiac disorders			Tachycardia; Palpitations	
Nervous system disorders		Dizziness; Headache	Dysgeusia; Somnolence	
Eye disorders		Dry eye	Blurred vision	
Ear and labyrinth disorders			Vertigo	
Respiratory, thoracic and mediastinal disorders		Dry throat	Pharyngolaryngeal pain; Cough; Nasal dryness	
Gastrointestinal disorders	Dry mouth	Abdominal pain; Diarrhoea; Dyspepsia; Constipation; Nausea	Abdominal discomfort; Flatulence, Gastroesophageal reflux	
Renal and urinary disorders		Dysuria	Urinary retention (including feeling of residual urine; micturition disorder); Urinary hesitation	
Skin and subcutaneous tissue disorders			Rash; Dry skin; pruritus	Angioedema; Urticaria
Infections and infestations			Urinary tract infection	
General disorders and administration site conditions			Fatigue	
Hepatobiliary disorders			ALT increased; GGT increased	
Psychiatric disorders		Insomnia		Confusional state

In clinical trials of fesoterodine, cases of markedly elevated liver enzymes were reported with the occurrence frequency no different from the placebo group. The relation to fesoterodine treatment is unclear.

Electrocardiograms were obtained from 782 patients treated with 4 mg, 785 treated with 8 mg, 222 treated with 12 mg fesoterodine and 780 with placebo. The heart rate corrected QT interval in fesoterodine treated patients did not differ from that seen in placebo treated patients. The incidence rates of QTc ≥ 500 ms post baseline or QTc increase of ≥ 60 ms is 1.9%, 1.3%, 1.4% and 1.5%, for fesoterodine 4 mg, 8 mg, 12 mg and placebo, respectively. The clinical relevance of these findings will depend on individual patient risk factors and susceptibilities present (see section 4.4).

Post-marketing cases of urinary retention requiring catheterization have been described, generally within the first week of treatment with fesoterodine. They have mainly involved elderly (≥ 65 years) male patients with a history consistent with benign prostatic hyperplasia (see section 4.4).

4.9 Overdose

Overdose with antimuscarinic agents, including fesoterodine can result in severe anticholinergic effects. Treatment should be symptomatic and supportive. In the event of overdose, ECG monitoring is recommended; standard supportive measures for managing QT prolongation should be adopted. Fesoterodine has been safely administered in clinical studies at doses up to 28 mg/day.

In the event of fesoterodine overdose, treat with gastric lavage and give activated charcoal. Treat symptoms as follows:

– Severe central anticholinergic effects (e.g. hallucinations, severe excitation): treat with physostigmine

- Convulsions or pronounced excitation: treat with benzodiazepines
- Respiratory insufficiency: treat with artificial respiration
- Tachycardia: treat with beta-blockers
- Urinary retention: treat with catheterisation
- Mydriasis: treat with pilocarpine eye drops and/or place patient in dark room.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Urinary antispasmodics, ATC code: G04B D11.

Fesoterodine is a competitive, specific muscarinic receptor antagonist. It is rapidly and extensively hydrolysed by non-specific plasma esterases to the 5-hydroxymethyl derivative, its primary active metabolite, which is the main active pharmacological principle of fesoterodine.

The efficacy of fixed doses of fesoterodine 4 mg and 8 mg was evaluated in two Phase 3 randomised, double-blind, placebo-controlled, 12-week studies. Female (79%) and male (21%) patients with a mean age of 58 years (range 19-91 years) were included. A total of 33% of patients were ≥ 65 years of age and 11% were ≥ 75 years of age.

Fesoterodine treated patients had statistically significant mean reductions in the number of micturitions per 24 hours and in the number of urge incontinence episodes per 24 hours at the end of treatment compared to placebo. Likewise, the response rate (% of patients reporting that their condition has been "greatly improved" or "improved" using a 4-point Treatment Benefit Scale) was significantly greater with fesoterodine compared to placebo. Furthermore, fesoterodine improved the mean change in the voided volume per micturition, and the mean change in the number of continent days per week (see Table 1 below).

Table 1: Mean changes from Baseline to end of treatment for primary and selected secondary endpoints

	Study 1				Study 2		
Parameter	**Placebo**	**Fesoterodine4 mg**	**Fesoterodine 8 mg**	**Active comparator**	**Placebo**	**Fesoterodine 4 mg**	**Fesoterodine 8 mg**
Number of micturitions per 24 hours#							
	N=279	N=265	N=276	N=283	N=266	N=267	N=267
Baseline	12.0	11.6	11.9	11.5	12.2	12.9	12.0
Change from baseline	-1.02	-1.74	-1.94	-1.69	-1.02	-1.86	-1.94
p-value		<0.001	<0.001			0.032	<0.001
Responder rate (treatment response)#							
	N=279	N=265	N=276	N=283	N=266	N=267	N=267
Responder rate	53.4%	74.7%	79.0%	72.4%	45.1%	63.7%	74.2%
p-value		<0.001	<0.001			<0.001	<0.001
Number of urge incontinence episodes per 24 hours							
	N=211	N=199	N=223	N=223	N=205	N=228	N=218
Baseline	3.7	3.8	3.7	3.8	3.7	3.9	3.9
Change from baseline	-1.20	-2.06	-2.27	-1.83	-1.00	-1.77	-2.42
p-value		0.001	<0.001			0.003	<0.001
Number of continent days per week							
	N=211	N=199	N=223	N=223	N=205	N=228	N=218
Baseline	0.8	0.8	0.6	0.6	0.6	0.7	0.7
Change from baseline	2.1	2.8	3.4	2.5	1.4	2.4	2.8

p-value		0.007	<0.001			<0.001	<0.001
Voided volume per micturition (ml)							
	N=279	N=265	N=276	N=283	N=266	N=267	N=267
Baseline	150	160	154	154	159	152	156
Change from baseline	10	27	33	24	8	17	33
p-value		<0.001	<0.001			0.150	<0.001

primary end points

Cardiac electrophysiology: The effect of fesoterodine 4 mg and 28 mg on the QT interval was thoroughly evaluated in a double-blind, randomised, placebo- and positive-controlled (moxifloxacin 400 mg) parallel group study with once-daily treatment over a period of 3 days in 261 male and female subjects aged 45 to 65 years. Change from baseline in QTc based on the Fridericia correction method did not show any differences between the active treatment and placebo group.

5.2 Pharmacokinetic properties

Absorption

After oral administration, due to rapid and extensive hydrolysis by non-specific plasma esterases, fesoterodine was not detected in plasma.

Bioavailability of the active metabolite is 52%. After single or multiple-dose oral administration of fesoterodine in doses from 4 mg to 28 mg, plasma concentrations of the active metabolite are proportional to the dose. Maximum plasma levels are reached after approximately 5 hours. Therapeutic plasma levels are achieved after the first administration of fesoterodine. No accumulation occurs after multiple-dose administration.

Distribution

Plasma protein binding of the active metabolite is low with approximately 50% bound to albumin and alpha ¯ 1-acid glycoprotein. The mean steady-state volume of distribution following intravenous infusion of the active metabolite is 169 l.

Metabolism

After oral administration, fesoterodine is rapidly and extensively hydrolysed to its active metabolite. The active metabolite is further metabolised in the liver to its carboxy, carboxy-N-desisopropyl, and N-desisopropyl metabolite with involvement of CYP2D6 and CYP3A4. None of these metabolites contribute significantly to the antimuscarinic activity of fesoterodine. Mean C_{max} and AUC of the active metabolite are 1.7 and 2-fold higher, respectively, in CYP2D6 poor metabolisers as compared to extensive metabolisers.

Elimination

Hepatic metabolism and renal excretion contribute significantly to the elimination of the active metabolite. After oral administration of fesoterodine, approximately 70% of the administered dose was recovered in urine as the active metabolite (16%), carboxy metabolite (34%), carboxy-N-desisopropyl metabolite (18%), or N-desisopropyl metabolite (1%), and a smaller amount (7%) was recovered in faeces. The terminal half-life of the active metabolite following oral administration is approximately 7 hours and is absorption rate-limited.

Age and gender

No dose adjustment is recommended in these subpopulations. The pharmacokinetics of fesoterodine are not significantly influenced by age and gender.

Paediatric patients

The pharmacokinetics of fesoterodine have not been evaluated in paediatric

patients. Renal impairment

In patients with mild or moderate renal impairment (GFR 30 – 80 ml/min), C_{max} and AUC of the active metabolite increased up to 1.5 and 1.8-fold, respectively, as compared to healthy subjects. In patients with severe renal impairment (GFR < 30 ml/min), C_{max} and AUC are increased 2.0 and 2.3-fold, respectively.

Hepatic impairment

In patients with moderate hepatic impairment (Child Pugh B), C_{max} and AUC of the active metabolite increased 1.4 and 2.1-fold, respectively, as compared to healthy subjects. Pharmacokinetics of fesoterodine in patients with severe hepatic impairment have not been studied.

5.3 Preclinical safety data

In non-clinical safety pharmacology, general toxicity, genotoxicity and carcinogenicity studies no clinically relevant effects have been observed, except those related to the pharmacological effect of the active substance.

Reproduction studies have shown minor embryotoxicity at doses close to maternally toxic ones (increased number of resorptions, pre-implantation and post-implantation losses).

Supratherapeutic concentrations of the active metabolite of fesoterodine, have been shown to inhibit K^+ current in cloned human ether-à-go-go-related gene (hERG) channels and prolong action potential duration (70% and 90% repolarisation) in canine isolated Purkinje fibres. However in conscious dogs, the active metabolite had no effect on the QT interval and QTc interval at plasma exposures at least 33 ¯ fold higher than mean peak free plasma concentration in human subjects who are extensive metabolisers and 21 ¯ fold higher than measured in subjects who are poor CYP2D6 metabolisers after fesoterodine 8 mg once daily.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Xylitol

Lactose monohydrate

Microcrystalline cellulose

Hypromellose

Glycerol dibehenate

Talc

Film-coat

Polyvinyl alcohol

Titanium dioxide (E171)

Macrogol (3350)

Talc

Soya lecithin

Indigo carmine aluminium lake (E132)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 25°C.

Store in the original package to protect from moisture.

6.5 Nature and contents of container

TOVIAZ 4 mg tablets and TOVIAZ 8 mg tablets are packed in aluminium-aluminium blisters in cartons containing 7, 14, 28, 56, 84, 98 or 100 tablets. In addition, TOVIAZ 4 mg and 8mg tablets are also packed in HDPE bottles containing 30 or 90 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Pfizer Limited

Ramsgate Road

Sandwich

Kent CT13 9NJ

United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/386/001-018

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

20/04/2007

10. DATE OF REVISION OF THE TEXT

03/2011

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

11. LEGAL CATEGORY

POM

A 12 week, single centre, open label study to evaluate the effect of fesoterodine flexible dosing regimen on the sexual function of women with overactive bladder.

Protocol Summary

Background and Rationale

The Overactive bladder Syndrome (OAB) is the term used to describe the symptom complex of urinary urgency with or without urge incontinence, usually with frequency and nocturia[1]. It is reported that the prevalence of OAB in the general population is 14-16%[2]. OAB is a distressing problem that can seriously affect an individual's quality of life by forcing them to alter their social, physical, occupational and sexual activities. Anticholinergic drugs (also known as antimuscarinics) are the mainstay of treatment for OAB symptoms. In the UK in 2007, 2.85 million prescriptions were written for anticholinergic drugs[3]. Fesoterodine fumarate is a new addition to this class of drug and is available as sustained release tablets in flexible dosing (4mg and 8mg).

Several reports have shown the negative impact of OAB on sexual health. Rogers et al[4] compared sexual function in women with and without urinary Incontinence (UI) and/or pelvic organ prolapse (POP) using a validated condition-Specific questionnaire, the Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire (PISQ), and concluded that PISQ scores were significantly lower among women with UI/POP than in those without (P = 0.003). Women with UI/POP have poorer sexual functioning, as measured by the PISQ, and report less frequent sexual activity. In addition, women with UI/POP are more likely to restrict sexual activity for fear of incontinence. Women with POP and UI are more likely to report decreased libido, decreased sexual excitement, and difficulty achieving orgasm during intercourse when compared to women with UI alone[5]. Yib et al[6] showed that marital relationships and sexual function were negatively affected in women who had urinary stress incontinence (USI) or detrusor overactivity (DO). In a report to study the relation between different types of incontinence and sexual health, Urwitz-Lane[7] showed that among sexually active women with urinary incontinence, sexual function as assessed by the PISQ-12 does not differ according to type of incontinence.

Some studies have reported that antimuscarinics have a positive impact on sexual health. Hajebrahimi et al[8] evaluated the impact of tolterodine IR on sexual function in patients with OAB. A total of 30 sexually active women with OAB from 20 to 52 years were included. All patients filled out the International Consultation on Incontinence Questionnaire (ICIQ) and the Arizona Sexual Experience Scale (ASEX) before treatment and at the end of each month of treatment until 3 months. The results showed an improvement in the mean total ASEX score relative to baseline at the first ($P<0.01$), second ($P<0.01$), and third ($P<0.01$) follow-ups. The mean scores for sexual desire, arousal, vaginal lubrication, orgasm, and orgasm satisfaction improved significantly ($P<0.01$) with each follow-up. They concluded that tolterodine IR significantly improves sexual function of women with OAB. Improvement is seen in all domains of sexual function. In another report, Rogers et al[9] evaluated the impact of extended release (ER) tolterodine on sexual health and anxiety scores in women with OAB. 413 women were randomised to either tolterodine ER or placebo. Assessments used included bladder diaries, the Sexual Quality of Life Questionnaire – Female (SQOL-F), Pelvic Organ prolapse / Urinary Incontinence Sexual Questionnaire (PISQ) and the Hospital Anxiety and Depression (HAS) scale. Overall the study found that OAB symptoms improved with tolterodine ER as well as an improvement in the sexual health and anxiety scores.

As fesoterodine is relatively new to the UK market there are currently no clinical trials looking at its impact on sexual function. This study is funded by an Investigator Initiated grant from Pfizer Ltd.

Objectives and Endpoints

Null Hypothesis

Fesoterodine has no effect on sexual function in women complaining of overactive bladder syndrome.

Primary Objective

The primary objective is to assess the impact on sexual function, of 12 weeks flexible dose fesoterodine in women with OAB compared to baseline.

Secondary Objectives

- To assess the use of flexible dosing of fesoterodine on micturition frequency per 24 hours, nocturnal micturitions per 24 hours, urinary urgency incontinence episodes per 24 hours and urgency episodes per 24 hours after 12 weeks compared to baseline.
- To assess the effect of flexible dose fesoterodine on treatment satisfaction and health related quality of life measure at 12 weeks compared to baseline.
- To assess the tolerability of flexible dose fesoterodine in women with OAB.
- To assess the impact of fesoterodine on bowel function.

Primary Endpoint

Change in item scores of the Pelvic Organ Prolapse and Urinary Incontinence Sexual Questionnaire – short form (PISQ-12) and the Sexual Quality of Life questionnaire (SQOL) at week 12 relative to baseline.

Secondary Endpoints

Bladder Diary

- Change in mean number of micturitions per 24hours at week 12 relative to baseline.
- Change in mean number of nocturnal micturitions per 24 hours at week 12 relative to baseline in subjects with >0 episodes during the 3-day baseline diary period. (Nocturnal micturitions are defined as those occurring between the time the subject goes to bed with the intention of sleeping and the time she rises to start the next day).
- Percentage change in urinary urgency incontinence (UUI) episodes per 24 hours at week 12 relative to baseline in subjects with >0 UUI episodes during the 3-day baseline diary period.

- Change in mean number of urgency episodes per 24 hours at week 12 relative to baseline. (Urgency episodes are defined as those with a Patient Perception of Intensity of Urgency Score (PPIUS) rating of ≥3 in the diary.
- Percentage change in urgency episodes per 24 hours at week 12 relative to baseline.

Patient Questionnaires

Patient Perception of Bladder Condition (PPBC)

- Change in PPBC at week 12 relative to baseline.

King's Health Questionnaire (KHQ)

- Change in total score of each domain at week 12 relative to baseline.

Patient Assessment of Constipation Quality of Life Questionnarie (PAC-QOL)

- Change in total score of each domain at week 12 relative to baseline

Self Assessment Goal Achievement Questionnaire (SAGA)

- Achievement of patient orientated goals at 12 weeks relative to baseline.

Assessments

This is a single centre open label study which will aim to enter 130 female subjects with OAB symptoms. The study will be carried out at the Urogynaecology department at King's College Hospital, London.

Sexual function and efficacy assessments will be evaluated via 3-day bladder diaries and questionnaires (KHQ, PISQ-12, SQoL, PAC-QoL, SAGA, PPBC). Tolerability and safety will be evaluated at every visit with recording of adverse events.

Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be eligible for enrolment into the trial.

1. Female outpatients aged 18 – 80 years.

2. Overactive bladder symptoms (subject reported) for ≥3 months prior to screening visit according to ICS guidelines.
3. Mean urinary frequency of ≥8 micturitions per 24 hours as verified by the screening bladder diary prior to baseline / Visit 2.
4. Mean number of Urgency episodes ≥3 per 24 hours as verified by the screening bladder diary prior to baseline / Visit 2.
5. Sexually active with a mean frequency of sexual activity ≥1 per week.
6. Able and willing to complete the micturition bladder diaries and all trial related questionnaires, comply with scheduled clinic visits and clinical trial procedures.
7. Capability of understanding and having signed the informed consent form after full discussion of the treatment and its risks and benefits.

Exclusion Criteria

Subjects presenting with any of the following will not be included in the trial.

1. Any condition that would contraindicate the use of fesoterodine including, but not limited to: hyposensitivity to the active substance (fesoterodine fumarate) or any of the excipients, or to peanut or soya; urinary retention; gastric retention; uncontrolled narrow angle glaucoma; myasthesia gravis; moderate or severe hepatic impairment (Child Pugh C); severe renal impairment; severe ulcerative colitis; and toxic megacolon.
2. Stage 3 or greater pelvic organ prolapse, defined as tissue protuding to or beyond the introitus in lithotomy position at rest (without increase in intra abdominal pressure).
3. History of lower urinary tract surgery (eg. Incontinence surgery, diverticulectomy, OTIS urethrotomy) with the exception of any minor surgery (eg. Cystoscopic procedures).
4. A known history of interstitial cystitis or a significant pain component associated with OAB symptoms, uninvestigated haematuria, urogenital cancer, interstitial or external radiation to the pelvis or external genitalia, or bladder outlet obstruction, radiation cystitis, genitor-urinary tuberculosis, bladder calculi, urethral obstruction or detrusor-sphincter dysynergia.
5. Subjects with bladder stones. Subjects with a previous history of bladder stones may be included.

6. Previous history of acute urinary retention requiring catheterisation, clinically relevant bladder outlet obstruction or severe voiding difficulties in the judgement of the investigator prior to Visit 2 (baseline).
7. Use of an indwelling or an intermittent self-catheterisation programme.
8. Symptoms of incontinence being predominantly stress urinary incontinence as determined by the investigator.
9. Urinary tract infection (UTI) as shown by the results of the urinalysis at screening or recurrent urinary tract infections (RUTIs) defined as treatment for UTI ≥3 times in the last year.
10. Use of any electrostimulation, bladder training, or pelvic floor exercises (with certified incontinence practitioners) within 4 weeks prior to Visit 1 (Screening).
11. Treatment with antimuscarinic OAB medication with 2 weeks prior to Visit 2 (baseline), including any preparation containing: darifenacin, oxybutynin, propiverine, tolterodine, fesoterodine, solifenacin and trospium.
12. Initiation of treatment during the 12 week trial period with:
    a. Any drug treatment for OAB
    b. Any drugs with significant anticholinergic, antispasmodic, parasympathetic, or cholinergic agonistic effects
13. Intermittent or unstable use of diuretics or alpha blockers, or tricyclic antidepressants, oestrogen therapy and any 5AR inhibitors or initiation of such treatment(s) within 2 weeks prior to Visit 2 (baseline).
14. Treatment with moderate or potent CYP3A4 inhibitors, such as grapefruit juice, macrolide antibiotics (erythromycin, clarithromycin), immunosuppressants (cyclosporine), azole antifungal agents (ketonazole, itraconazole), protease inhibitors within 3 weeks prior to Visit 2 (baseline), or the expectation to start such a treatment during the trial.
15. Administration of medication capable of inducing hepatic enzyme metabolism or transport (eg barbiturates, rifampicin, carbemazipine, phenytoin, primidone, or St John's Wort).
16. Participated in any clinical trial or received an investigation drug within 4 weeks prior to Visit 2.
17. History of alcohol abuse and /or any other drug in the opinion of the investigator.

18. Female subjects who are pregnant, nursing, or who are intending to become pregnant during the trial or within three months after the completion of the trial.
19. Female subjects of childbearing potential who are heterosexually active but not using an adequate form of contraception. Reliable contraception methods defined as hormonal methods of contraception (including oral, patches, injected, implants, IUDs, condom with spermicidal foam/gel/film/cream/suppository, tubal ligation male partner who has had a vasectomy for a least 4 months.
20. Subjects who have any medical (including known history of major haematological, renal, cardiovascular or hepatic abnormalities) or psychological condition or social circumstances that would impair their ability to participate reliably in the trial, or those who may increase the risk to themselves or others by participating.
21. Has any current malignancy except
    a. Those ≥5 years ago without recurrence
    b. Excised basal cell skin carcinoma or squamous cell cancer
22. Subjects who, in the opinion of the investigator, are not likely to complete the trial for any reason.

Statistical Methods

Wilcoxon Signed Ranks will be used to compare baseline and 12 week KHQ, Pac-QoL, SQoL and PISQ-12.

Comparisons of the difference in baseline and 12 week PPBC scores will also be analysed.

References

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9. Rogers R, Bachmann G, Jumadilova Z, Sun F, Morrow JD, Guan Z, Bavendam T Efficacy of tolterodine on overactive bladder symptoms and sexual and emotional quality of life in sexually active women. Curr Med Res Opin. 2009 Jul 14

Schedule of Activities

Protocol Activity	**Visit 1** **Screening** **-14 days** **(±7days)**	**Visit 2** **Baseline** **Week 0**	**Visit 3** **End of** **Week 4** **(±7days)**	**Visit 4** **End of Tx** **Week 12** **(or early termination)** **(±7days)**
Written informed consent	X	X		
Demographics & Medical History		X		
Physical exam		X		
Inclusion / exclusion criteria		X		
Body mass index (BMI)		X		
Urine dipstick test and post void residual measurement		X		
Urine pregnancy test for women of child bearing potential		X		X
Menopausal status		X		X
PISQ-12		X		X
SQoL		X		X
PPBC		X		X
KHQ		X		X
PAC-QoL		X		x
SAGA		X		X
Dispense 3 day bladder diary & PPIUS	X	X	X	
Evaluation of bladder diary & PPIUS		X	X	X
Adverse events		X	X	X
Concomitant medication and non drug treatment	X	X	X	X
Dose assessment and titration			X	
Dispense study medication		X	X	
Study medication return / count			X	X
Assess drug compliance			X	X

PROTOCOL TITLE:

A 12 week, multi centre, open label study to evaluate the effect of fesoterodine flexible dosing regimen on the sexual function of women with overactive bladder.

Trial Identifiers

EudraCT Number 2010-023851-27

ISRCTN – 40720691

Sponsor

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CONTENTS

1. Background & Rationale

The Overactive bladder Syndrome (OAB) is the term used to describe the symptom complex of urinary urgency with or without urge incontinence, usually with frequency and nocturia[1]. It is reported that the prevalence of OAB in the general population is 14-16%[2]. OAB is a distressing problem that can seriously affect an individual's quality of life by forcing them to alter their social, physical, occupational and sexual activities. Anticholinergic drugs (also known as antimuscarinics) are the mainstay of treatment for OAB symptoms. In the UK in 2007, 2.85 million prescriptions were written for anticholinergic drugs[3]. Fesoterodine fumarate is a new addition to this class of drug and is available as prolonged release tablets in flexible dosing (4mg and 8mg).

Several reports have shown the negative impact of OAB on sexual health. Rogers et al[4] compared sexual function in women with and without Urinary Incontinence (UI) and/or pelvic organ prolapse (POP) using a validated condition-specific questionnaire, the Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire (PISQ), and concluded that PISQ scores were significantly lower among women with UI/POP than in those without (P = 0.003). Women with UI/POP have poorer sexual functioning, as measured by the PISQ, and report less frequent sexual activity. In addition, women with UI/POP are more likely to restrict sexual activity for fear of incontinence. Women with POP and UI are more likely to report decreased libido, decreased sexual excitement, and difficulty achieving orgasm during intercourse when compared to women with UI alone[5]. Yib et al[6] showed that marital relationships and sexual function were negatively affected in women who had urinary stress incontinence (USI) or detrusor overactivity (DO). In a report to study the relation between different types of incontinence and sexual health, Urwitz-Lane[7] showed that among sexually active women with urinary incontinence, sexual function as assessed by the PISQ-12 (shortened version of the PISQ) does not differ according to type of incontinence.

Some studies have reported that antimuscarinics have a positive impact on sexual health. Hajebrahimi et al[8] evaluated the impact of tolterodine Immediate Release (IR) on sexual function in patients with OAB. A total of 30 sexually active women with OAB from 20 to 52 years were included. All patients filled out the International Consultation on Incontinence Questionnaire (ICIQ) and the Arizona Sexual Experience Scale (ASEX) before treatment and at the end of each month of treatment until 3 months. The results showed an improvement in the mean total ASEX score relative to baseline at the first ($P<0.01$), second ($P<0.01$), and third ($P<0.01$) follow-ups. The mean scores for sexual desire, arousal, vaginal lubrication, orgasm, and orgasm satisfaction improved significantly ($P<0.01$) with each follow-up. They concluded that tolterodine IR significantly improves sexual function of women with OAB. Improvement is seen in all domains of sexual function. In another report, Rogers et al[9] evaluated the impact of extended release (ER) tolterodine on sexual health and anxiety scores in women with OAB. 413 women were randomised to either tolterodine ER or placebo.
Assessments used included bladder diaries, the Sexual Quality of Life Questionnaire – Female (SQOL-F), Pelvic Organ prolapse / Urinary Incontinence Sexual Questionnaire (PISQ) and the Hospital Anxiety and Depression (HAD) scale. Overall the study found that OAB symptoms improved with tolterodine ER as well as an improvement in the sexual health and anxiety scores. However, improvements in sexual function were not the primary outcomes for these studies.

Fesoterodine is a relatively new antimuscarinic to the UK market and there are currently no clinical trials looking at its impact on sexual function.

This trial will be conducted in compliance with the principles of the Declaration of Helsinki and the principles of-GCP. The protocol has been submitted for approval by an NHS Research Ethics Committee (REC).

2 Trial Objectives and Design

2.1. Trial Objectives

Null Hypothesis

Fesoterodine has no effect on sexual function in women complaining of overactive bladder syndrome.

Primary Objective

The primary objective is to assess the impact on sexual function, after 12 weeks flexible dose fesoterodine in women with OAB compared to baseline.

Secondary Objectives

- To assess the use of flexible dosing of fesoterodine on micturition frequency per 24 hours, nocturnal micturitions per 24 hours, urinary urgency incontinence episodes per 24 hours and urgency episodes per 24 hours after 12 weeks compared to baseline.
- To assess the effect of flexible dose fesoterodine on treatment satisfaction and health related quality of life measure at 12 weeks compared to baseline.
- To assess the tolerability of flexible dose fesoterodine in women with OAB.
- To assess the impact of fesoterodine on bowel function.
- To assess if changes in sexual function are independent of urodynamic variables

Primary Endpoint

Change in item scores of the Pelvic Organ Prolapse and Urinary Incontinence Sexual Questionnaire – short form (PISQ-12) and the Sexual Quality of Life

questionnaire (SQOL) at week 12 relative to baseline.

Secondary Endpoints

Bladder Diary

- Change in mean number of micturitions per 24hours at week 12 relative to baseline.
- Change in mean number of nocturnal micturitions per 24 hours at week 12 relative to baseline in subjects with >0 episodes during the 3-day baseline diary period. (Nocturnal micturitions are defined as those occurring between the time the subject goes to bed with the intention of sleeping and the time she rises to start the next day).
- Percentage change in urinary urgency incontinence (UUI) episodes per 24 hours at week 12 relative to baseline in subjects with >0 UUI episodes during the 3-day baseline diary period.
- Change in mean number of urgency episodes per 24 hours at week 12 relative to baseline. (Urgency episodes are defined as those with a Patient Perception of Intensity of Urgency Score (PPIUS) rating of ≥2 in the diary.
- Percentage change in urgency episodes per 24 hours at week 12 relative to baseline.

Subtracted Cystometry (in forty subjects only)

- Change in first sensation
- Change in maximum cystometric capacity
- Change in time to first detrusor contraction
- Presence of detrusor overactivity

Patient Questionnaires

Patient Perception of Bladder Condition (PPBC)

- Change in PPBC at week 12 relative to baseline.

King's Health Questionnaire (KHQ)

- Change in total score of each domain at week 12 relative to baseline.

Patient Assessment of Constipation Quality of Life Questionnaire (PAC-QOL)

- Change in total score of each domain at week 12 relative to baseline

Self Assessment Goal Achievement Questionnaire (SAGA)

- Achievement of patient orientated goals at 12 weeks relative to baseline.

2.2 Trial Design

This is a multi centre open label study which will aim to enter 132 female subjects with OAB symptoms. The study will be carried out at the Urogynaecology department at King's College Hospital, London and St. Mary's Hospital, Paddington, Medway Maritime Hospital, Kent and Croydon University Hospital, London.

Sexual function and efficacy assessments will be evaluated via 3-day bladder diaries, questionnaires (KHQ, PISQ-12, SQoL, PAC-QoL, SAGA, PPBC) and urodynamics. Tolerability and safety will be evaluated at every visit with recording of adverse events.

2.3 Trial Flowchart

Protocol Activity	Visit 1 Screening -14 days (±7days)	Visit 2 Baseline Week 0	Visit 3 End of Week 4 (±7days)	Visit 4 End of Tx Week 12 (or early termination) (±7days)	Telephone Follow up Week 24
Written informed consent	X				
Demographics & Medical History	X				
Physical exam	X				
Inclusion / exclusion criteria	X	X			
Body mass index (BMI)	X				
Urine dipstick test and post void residual measurement	X				
Urine pregnancy test for women of child bearing potential	X			X	
Menopausal status	X			X	
PISQ-12		X		X	
SQoL		X		X	
PPBC		X		X	
KHQ		X		X	
PAC-QoL		X		X	
SAGA		X		X	
Dispense 3 day bladder diary & PPIUS	X	X	X		
Evaluation of bladder diary & PPIUS		X	X	X	

Adverse events		**X**	**X**	**X**	**x**
Concomitant medication and non drug treatment	**X**	**X**	**X**	**X**	
Dose assessment and titration			**X**		
Dispense study medication		**X**	**X**		
Study medication return / count			**X**	**X**	
Subtracted cystometry				**X (forty women only)**	
Assess drug compliance			**X**	**X**	**x**
Assess treatment continuation					**x**

3 Trial Medication

3.1 Investigational Medicinal Product

Fesoterodine fumarate is an antimuscarinic agent developed for the treatment of the symptoms that may occur in patients with OAB syndrome. Fesoterodine was granted a marketing authorization in Europe in May 2007. It is manufactured and supplied by Pfizer Ltd.

The study drug will be supplied in two different strengths as described below:

- Fesoterodine fumarate prolonged release 4mg tablets
- Fesoterodine fumarate prolonged release 8mg tablets

Festerodine commercial stock will be ordered in and used for trial patients.

Product name	Colour	Strength	Dosage form	Package form	Route of administration
Fesoterodine fumarate	Light blue	4mg	Prolonged release tablet	blister packs	Oral
Fesoterodine fumarate	blue	8mg	Prolonged release tablet	blister packs	Oral

3.2 Dosing Regimen

The study drug will be dispensed according to the following schedule:

Visit 2 (Week 0) – 28 tabs of 4mg tablets

Visit 3 (Week 4) –56 tabs of 4mg tablets or 56 tabs of 8mg tablets, depending on the dose selection for each individual subject at this visit (based upon a discussion between the subject and the investigator of the efficacy and tolerability reported by the subject, the investigator will either increase the dose to 8mg for those subjects who desire greater symptom improvement and report good tolerability, or will continue the subject on the 4mg dose for the remaining 8 weeks of the study).

No dose adjustments will be allowed after visit 3 during the last eight weeks of the treatment phase.

One tablet should be taken with water at approximately the same time every day. It should be swallowed whole without chewing. Fesoterodine can be administered with or without food.

3.3 Drug Accountability

All Investigational Medicinal Product (IMP) supplies will be stored in accordance

with applicable regulatory requirements.

The investigator will be responsible for recording the receipt, administration and return of all trial medication, and for ensuring the supervision (via the hospital pharmacy) of the storage and allocation of trial medication. A complete inventory will be performed of the trial medication upon delivery to the site.

Overall IMP accountability logs will be completed during the trial. The subject must return all trial medication, whether full, partially full or empty, to the investigator and the investigator must retain these packs at the site until accountability has been completed. At the end of the trial excess IMP will be destroyed and adequately documented.

3.4 Subject Compliance.

Subjects must be informed by the investigator that it is extremely important to take their daily study medication as instructed. Subjects will return all medication packs at Visits 3 and 4 and compliance assessed. The investigator will review the amount of unused medication and assess whether this is consistent with the dosing instructions and the time between visits. The investigator will record the number of doses missed or extra doses taken and the reasons why directly into the CRF if this information is available.

Lack of study compliance is defined as one or more of the following:

- Less than 80% or greater than 120% study medication compliance

If the tablet count of the returned medication indicates that the subject has not taken all prescribed study drug, the subject should be counselled about the importance of compliance and how to take study medication.

If the subject has been non-compliant in any area defined above, the subject's participation in the study should be re-evaluated.

3.5 Concomitant Medication

All medications with the exceptions of those listed below will be permitted concurrently with the study medication. If a patient needs to start one of the excluded medications during the study they will be withdrawn.

1. Treatment with antimuscarinic OAB medication within 2 weeks prior to Visit 2 (baseline), including any preparation containing: darifenacin, oxybutynin, propiverine, tolterodine, fesoterodine, solifenacin and trospium. If any of these preparations are started during the study the patient will be withdrawn.
2. Initiation of treatment during the 12 week trial period with:
    a. Any other drug treatment for OAB including all the antimuscarinics listed in point 1
    b. Any drugs with significant anticholinergic, antispasmodic, parasympathetic, or cholinergic agonistic effects
3. Intermittent or unstable use of diuretics or alpha blockers, or tricyclic antidepressants, oestrogen therapy and any 5AR inhibitors or initiation of such treatment(s) within 2 weeks prior to Visit 2 (baseline) or during the study.
4. Treatment with moderate or potent CYP3A4 inhibitors, such as grapefruit juice, macrolide antibiotics (erythromycin, clarithromycin), immunosuppressants (cyclosporine), azole antifungal agents (ketonazole, itraconazole), protease inhibitors within 3 weeks prior to Visit 2 (baseline), or the expectation to start such a treatment during the trial.
5. Administration of medication capable of inducing hepatic enzyme metabolism or transport (eg. rifampicin, carbamazepine, phenobarbital, phenytoin, or St John's Wort) at any point during the study or within the

6 weeks prior to Visit 2 (baseline).

6. Treatment with potent CYP2D6 inhibitors such as bupropion, cinacalcet, fluoxetine, paroxetine or quinine at any point during the study

4 Selection and Withdrawal of Subjects

4.1 Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be eligible for enrolment into the trial.

1. Female outpatients aged 18 – 80 years.
2. Overactive bladder symptoms (subject reported) for ≥3 months prior to screening visit according to ICS guidelines.
3. Mean number of Urgency episodes ≥3 per 24 hours as verified by the screening bladder diary prior to baseline / Visit 2.
4. Sexually active
5. Able and willing to complete the micturition bladder diaries and all trial related questionnaires, comply with scheduled clinic visits and clinical trial procedures.
6. Capability of understanding and having signed the informed consent form after full discussion of the treatment and its risks and benefits.
7. Able to speak, read and write in English.

4.2 Exclusion Criteria

Subjects presenting with any of the following will not be included in the trial.

1. Any condition that would contraindicate the use of fesoterodine including, but not limited to: hyposensitivity to the active substance (fesoterodine fumarate) or any of the excipients, or to peanut, lactose or soya; urinary retention; gastric retention; uncontrolled narrow angle glaucoma; myasthesia gravis; moderate or severe hepatic impairment; severe renal impairment; severe ulcerative colitis; and toxic megacolon.

2. Stage 3 or greater pelvic organ prolapse, defined as tissue protuding to or beyond the introitus in lithotomy position at rest (without increase in intra abdominal pressure).
3. History of lower urinary tract surgery (eg. Incontinence surgery, diverticulectomy, OTIS urethrotomy) with the exception of any minor surgery (eg. Cystoscopic procedures).
4. A known history of interstitial cystitis or a significant pain component associated with OAB symptoms, uninvestigated haematuria, urogenital cancer, interstitial or external radiation to the pelvis or external genitalia, or bladder outlet obstruction, radiation cystitis, genitor-urinary tuberculosis, bladder calculi, urethral obstruction or detrusor-sphincter dysynergia.
5. Subjects with bladder stones. Subjects with a previous history of bladder stones may be included.
6. Previous history of acute urinary retention requiring catheterisation, clinically relevant bladder outlet obstruction or severe voiding difficulties in the judgement of the investigator prior to Visit 2 (baseline).
7. Use of an indwelling or an intermittent self-catheterisation programme.
8. Symptoms of incontinence being predominantly stress urinary incontinence as determined by the investigator.
9. Urinary tract infection (UTI) as shown by the results of the urinalysis at screening or recurrent urinary tract infections (RUTIs) defined as treatment for UTI ≥3 times in the last year.
10. Use of any electrostimulation, bladder training, or pelvic floor exercises (with certified incontinence practitioners) within 4 weeks prior to Visit 1 (Screening).
11. Treatment with antimuscarinic OAB medication with 2 weeks prior to Visit 2 (baseline), including any preparation containing: darifenacin, oxybutynin, propiverine, tolterodine, fesoterodine, solifenacin and trospium.
12. Initiation of treatment during the 12 week trial period with:

a. Any other drug treatment for OAB
b. Any drugs with significant anticholinergic, antispasmodic, parasympathetic, or cholinergic agonistic effects

13. Intermittent or unstable use of diuretics or alpha blockers, or tricyclic antidepressants, oestrogen therapy and any 5AR inhibitors or initiation of such treatment(s) within 2 weeks prior to Visit 2 (baseline).
14. Use of potent CYP3A4 inhibitors, such as grapefruit juice, macrolide antibiotics (erythromycin, clarithromycin), immunosuppressants (cyclosporine), azole antifungal agents (ketonazole, itraconazole), protease inhibitors within 3 weeks prior to Visit 2 (baseline), or the expectation to start any during the trial.
15. Administration of medication capable of inducing hepatic enzyme metabolism or transport (eg rifampicin, carbamazepine, phenytoin, phenobarbital, or St John's Wort) at any point in the study or within the 6 weeks prior to Visit 2 (baseline).
16. Treatment with potent CYP2D6 inhibitors such as bupropion, cinacalcet, fluoxetine, paroxetine or quinine at any point during the study
17. Participated in any interventional clinical trial or received an investigational drug within 4 weeks prior to Visit 2.
18. History of alcohol abuse and /or any other drug in the opinion of the investigator.
19. Female subjects who are pregnant, nursing, or who are intending to become pregnant during the trial or within three months after the completion of the trial.
20. Female subjects of childbearing potential who are heterosexually active but not using an adequate form of contraception. Reliable contraception methods defined as hormonal methods of contraception (including oral, patches, injected, implants, IUDs, condom with spermicidal foam/gel/film/cream/suppository, tubal ligation male partner who has had a vasectomy for a least 4 months).

21. Subjects who have any medical (including known history of major haematological, renal, cardiovascular or hepatic abnormalities) or psychological condition or social circumstances that would impair their ability to participate reliably in the trial, or those who may increase the risk to themselves or others by participating.
22. Has any current malignancy except
    c. Those ≥5 years ago without recurrence
    d. Excised basal cell skin carcinoma or squamous cell cancer
23. Subjects who, in the opinion of the investigator, are not likely to complete the trial for any reason.
24. Subjects with an uncontrolled cardiac arrhythmia or congestive heart failure.

4.3 Selection of Participants

Patients will be recruited from the urogynaecology clinics at King's College Hospital NHS Foundation Trust and St. Mary's Hospital (Imperial College Healthcare NHS Trust) and referred from Guy's and St Thomas' NHS Foundation Trust. These clinics include general outpatients, urodynamics and nurse led clinics. All patients that enter the trial will have had urodynamics performed as part of their routine care in the department prior to entry.

4.4 Randomisation Procedure / Code Break

No randomisation will take place in this study therefore there will be no need for a code break procedure. Subjects who meet all the inclusion and exclusion criteria listed will be administered the trial treatment.

4.5 Withdrawal of Subjects

The investigator may decide to take the subject out of the study if:

- They do not follow the directions of the study doctor
- They develop a serious illness that is not related to taking part in the study
- The investigator decides that the study is not in the subjects best interest
- Regulatory Authorities, or Research Ethics Committee, decide to stop the study
- They become pregnant, intend to become pregnant, or are breast-feeding a child during this study
- If there are compliance issues
- If the subject withdraws consent
- If subjects no longer meet the inclusion / exclusion criteria

If subjects are taken out of the study they may undergo some tests if they consent to do so. These include:

- A completed bladder diary will be collected and evaluated
- Sitting blood pressure and pulse rate will be measured
- Women of child bearing potential will need to provide a sample of urine for a pregnancy test
- Subjects will be asked to complete 6 questionnaires which will take approximately 30 minutes
- Subjects will be asked if they have had any new symptoms or worsening of existing symptoms and if they have taken any new medication or treatments since their last visit.
- The investigator will review the amount of unused study medication the subject has returned to assess whether this has been taken correctly.

4.6 Expected Duration of Trial.

Participants will be receive active treatment in the trial for 12 weeks and will then have a telephone follow up at 24 weeks. The end of the trial is defined as the last patient last visit.

5 Trial Procedures

5.1 By Visit

If the subject agrees to take part in this study, after signing the informed consent form, the following tests will be carried out to determine whether they are eligible to take part in this study.

Visit 1 (Screening visit)

At the screening visit:

- Weight, medical history (including any medication and non-drug treatment) and demography will be taken.
- Sitting blood pressure and pulse will be taken
- A physical examination will be conducted by a physician
- subjects will provide a sample of urine for the following-:
    - A urine dipstick test will be performed on a sample of urine to exclude blood and infection
    - A urine pregnancy test for women of child bearing potential will be performed
- Subjects will be issued with a 3-day bladder diary to complete and provided with instructions on how and when to complete the diary. The diary is provided for them to record details of the number of times they pass urine and related information and the completed diary will be collected at the next visit. The diary should be completed for the three (3) days prior to the next visit.
- Subjects will be provided with a questionnaire (SAGA) to help identify and help the study team understand what they would like to achieve in regards to their bladder conditions. They will also be provided with instructions on how to complete the questionnaire. Subjects will be able to review this at home and either complete this at home or complete it at the next visit.

If subjects meet all of the study entry requirements at this point and they agree to participate in the study, the clinic/research staff will ask them to return for Visit 2 (baseline visit).

A patient card will be provided to the subjects to act as an appointment reminder which will also include emergency contact details of the research team.

Visit 2 (Week 0) (Baseline)

At this visit, following assessment of eligibility by a delegated physician , subjects will be informed whether they are eligible to take part in this study. If they are eligible and still wish to participate, the next step is for them to have the baseline visit. Visits 1 and 2 can be combined if patients have completed a bladder diary as part of routine care and have received a patient information leaflet at least 48 hours prior to the appointment. In these cases, data from routine care prior to completion of a consent form may be used.

At the baseline visit-:

- A completed bladder diary will be collected and evaluated
- Subjects will be asked to complete 6 questionnaires which will take approximately 30 minutes (These can be completed at home if preferred)
- Subjects will be asked if they have had any new symptoms or worsening of existing symptoms and if they have taken any new medication or treatments since the last visit.
- Subjects will be given another 3-day diary (plus instructions) to complete the three days prior to the next visit (visit 3). The completed diary will be collected at the next visit.
- Subjects will be given a supply of IMP (fesoterodine 4mg) to take once a day at approximately the same time each day over the next 4 weeks.

Visit 3 (Week 4)

Four (4) weeks later subjects will return for visit 3. During this visit:

- A completed bladder diary will be collected and evaluated.
- Subjects will be asked if they have had any new symptoms or worsening of existing symptoms and if they have taken any new medication or treatments since their last visit.
- The investigator will review the amount of unused study medication subjects have

returned to assess compliance.

- Subjects will be given another 3-day diary (plus instructions) to complete the three days prior to the next visit (visit 4). The completed diary will be collected at the next visit.
- The dose of IMP will be reviewed by the study doctor and if applicable the dose maybe increased and recorded in notes and CRF.
- Subjects will be given a supply of IMP either fesoterodine 4 mg or fesoterodine 8 mg depending on discussions with the investigator.

Visit 4 (Week 12 End of Treatment or Early Termination Visit)

Eight (8) weeks later subjects will return for visit 4. During this visit:

- A completed bladder diary will be collected and evaluated
- Women of child bearing potential will need to provide a sample of urine for a pregnancy test
- Subjects will be asked to complete questionnaires which will take approximately 30 minutes (These can be completed at home prior if preferred).
- Subjects will be asked if they have had any new symptoms or worsening of existing symptoms and if they have taken any new medication or treatments since their last visit.
- The investigator will review the amount of unused study medication subjects have returned to assess compliance. .
- For those women who have consented to having urodynamics they will undergo subtracted cystometry at this visit. (This will only be for the first 40 subjects in the trial who consent to having subtracted cystometry performed at week 12)

Telephone Follow UP (24 Weeks)

- Subjects will be asked if they are still taking fesoterodine (as prescribed by their GP) or if they are taking any other anticholinergic medication or no therapy.
- If subjects have decided to stop all therapy they will be asked to explain their decision for this.
- Subjects will be asked if they have experienced any adverse events on completion of the trial.

Unscheduled Visits

During the course of the study subjects might have an additional visit for safety related issues. At this visit the following will be performed:

- Sitting blood pressure and pulse rate will be measured
- Subjects will be asked if they have had any new symptoms or worsening of existing symptoms and if they have taken any new medication or treatments since their last visit.
- The investigator will review the amount of unused study medication the subject has returned to assess whether this has been taken correctly.

5.2 Safety Monitoring - Laboratory Tests

A urine dipstick test for red blood cells, white blood cells, glucose, protein and nitrites will be performed by the investigator on site at the screening visit for trial qualification.

A urine pregnancy test (B-hCG) will be performed by the investigator on site at the screening visit for women of child bearing potential for trial qualification and at Visit 4.

6 Assessment of Efficacy

6.1.1 Primary Efficacy Parameters

Prolapse and Incontinence Sexual Quality of Life Questionnaire (PISQ-12) PISQ-12 is a self administered questionnaire consisting of 12 items.

Sexual Quality of Life Questionnaire (SQoL)

SQoL consists of a set of 18 statements, each asking about thoughts and feelings that subjects may have about their sex life. The statements may be positive or negative. Subjects respond on a 6-point Likert scale ranging from completely agree to completely disagree. It will be administered at visit 2 and 4.

6.1.2 Secondary Efficacy Parameters

Bladder Diary

Each subject will complete a bladder diary for 3 consecutive days immediately preceding each clinic visit to record details of micturitions (frequency, urgency, urgency urinary incontinence) as follows:

- Time arose and time went to bed
- Time of every micturition
- Volume of every micturition
- The subject will rate their feeling of urgency associated with each micturition episode using the 5 point Patient Perception of Intensity of Urgency score (PPIUS):

Patient Perception of Bladder Condition (PPBC)

PPBC is a self administered, single item, validated questionnaire that asks subjects to describe their perception of their bladder related problems. The PPBC will be administered at Visit 2 and 4.

King's Health Questionnaire (KHQ)

The KHQ is a self administered questionnaire containing 21 questions that are scored in nine domains (general health perception, incontinence impact, role limitations, physical limitations, social limitations, personal relationships, emotions, sleep/energy, severity of urinary symptoms). It will be administered at visit 2 and 4

Patient Assessment of Constipation Quality of Life (PAC-QoL)

A self administered questionnaire containing 28 items group into 4 subscales covering worries and concerns, physical discomfort, psychosocial discomfort and satisfaction. Responses are measured on a five point likert scale. It will be administered at visit 2 and 4.

Self Assessment Goal Acheivement Questionnaire (SAGA)

The SAGA questionnaire is a patient completed, physician reviewed tool to assess treatment goals and achievement of goals for subjects suffering from OAB and/or other urinary tract symptoms. The SAGA questionnaire is comprised of 2 parts.

The first SAGA assessment questionnaire will be provided to the subject at the end of screening visit, when the investigator should take time to explain the questionnaire. It rates the importance to the subject of her treatment goals. It contains 9 fixed goals and a further 5 open ended goals. The subject should complete the questionnaire at home prior to the baseline visit, prior to interacting

with the investigator. At visit 2, the subject and the investigator should review the competed questionnaire in order to assess whether the goals are realistic. If necessary, the investigator may explain to the subject that her goals are unrealistic and the subject must adjust/revise her selections before the questionnaire is finalised at visit 3.

The second part will be provided to the subject along with their SAGA first assessment (for reference). SAGA follow up questionnaire asks the subject to rate the degree of achievement of the subjects treatment goals set at the beginning of the treatment. There is also a one item measure relating to subjects rating the extent to which they have achieved all their goals set. It should be completed as the first activity of the final visit, prior to any interaction between the subject and the investigator.

Subtracted Cystometry (Urodynamics)

Subtracted cystometry measures the relationship between the detrusor pressure and bladder volume on filling and between the detrusor pressure and urine flow rate on voiding. During the procedure a pressure line and filling catheter are inserted into the bladder and a pressure line into the rectum (or vagina) and the bladder is filled with saline. Any changes of pressure in the bladder are recorded during this time. Once the bladder is full the filling catheter is removed. Patients may be asked to perform a cough provocation test to assess for stress incontinence and provoked detrusor overactivity . Finally patients will void into a flowmeter to assess the pressures within their bladder as they void. The test takes approximately 15 minutes.

This test will be performed at Visit 4 in the first forty subjects who have consent ed to this assessment. For all trial participants after this they will not have subtracted cystometry but will follow all other trial procedures. All patients entering the trial will have already had this procedure completed as part of their standard medical investigation. The data from this previous test for the forty patients will be used to compare against the visit 4 data.

6.2 Procedures for Assessing Efficacy Parameters

The investigator will review all of the completed questionnaires with the subjects

to ensure that they have been completed correctly.

The investigator will perform the subtracted cystometry on the sub group of women. The standard department protocol will be followed for all patients and the patients will be asked about bladder sensations during the test

6 Assessment of Safety

6.1 Specification, Timing and Recording of Safety Parameters.

A physical examination will be performed at the screening visit for assessment of trial qualification. Collection and reporting of AE will start following the first dose of the IMP until the last dose of the trial medication. Reporting of SAE's will continue until 28 days after stopping trial medication.

6.2 Procedures for Recording and Reporting Adverse Events

The Medicines for Human Use (Clinical Trials) Regulations 2004 and Amended Regulations 2006 gives the following definitions:

Adverse Event (AE): Any untoward medical occurrence in a subject to whom a medicinal product has been administered including occurrences which are not necessarily caused by or related to that product.

Adverse Reaction (AR): Any untoward and unintended response in a subject to an investigational medicinal product which is related to any dose administered to that subject.

Unexpected Adverse Reaction (UAR): An adverse reaction the nature and severity of which is not consistent with the information about the medicinal product in question set out in:

The summary of product characteristics (SmPC) for that product (for products with a marketing authorisation)

The Investigator's Brochure (IB) relating to the trial in question (for any other investigational product)

Serious adverse Event (SAE), Serious Adverse Reaction (SAR) or Unexpected Serious Adverse Reaction (USAR): Any adverse event, adverse reaction or unexpected adverse reaction, respectively, that

Results in death;

Is life-threatening;

Required hospitalisation or prolongation of existing hospitalisation;

Results in persistent or significant disability or incapacity;

Consists of a congenital anomaly or birth defect.

Important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above should also be considered serious.

Although not a serious adverse event, any unplanned pregnancy will also be reported via the SAE reporting system.

Reporting Responsibilities

King's College Hospital NHS Foundation Trust as sponsor has delegated the delivery of the Sponsor's responsibility for Pharmacovigilance (as defined in Regulation 5 of the Medicines for Human Use (Clinical Trials) Regulations 2004 to the King's Health Partners Clinical Trials Office (KHP-CTO). All reports of SAEs, SARs and SUSARs will be reviewed and signed by the Medical Investigator, for seriousness and causality.

All SAEs, SARs and SUSARs (excepting those specified in this protocol as not requiring reporting) will be reported immediately by the Chief Investigator to the (KHP-CTO) in accordance with the current Pharmacovigilance Policy.

The KHPCTO will report SUSARs (Suspected Unexpected Serious Adverse

Reactions) and other SARs to the regulatory authorities (MHRA, competent authorities of other EEA (European Economic Area) states in which the trial is taking place.

The Chief Investigator will report to the relevant ethics committees. Reporting timelines are as follows:

- SUSARs which are fatal or life-threatening must be reported not later than 7 days after the sponsor is first aware of the reaction. Any additional relevant information must be reported within a further 8 days.
- SUSARs that are not fatal or life-threatening must be reported within 15 days of the sponsor first becoming aware of the reaction.
- The Chief Investigator will provide a Development Safety Update Report (DSUR) which will be distributed to the KHP-CTO (on behalf of the sponsor), MHRA and the REC.

6.3 Treatment Stopping Rules

Examples include but are not limited to:

- Pregnancy
- Non-compliance
- Medical requirement to take contra indicated medication
- Hypersensitivity

7 Statistics

This is an open label study and no blinding will take place. There is no evidence to suggest selection or performance bias as all participants will initially be assigned the same dose of medication for the first 4 weeks of the study before they are offered the option to dose escalate for the remaining 8 weeks of the trial. All subjects will be treated equally throughout. However, as this study is not placebo controlled, it will not possible to assess the potential of the placebo

effect.

There are a total of 6 questionnaires to be completed on two occasions during the study. This may introduce an element of questionnaire fatigue or respondent burden. All patients will be informed of what is required of them during the trial and all the questionnaires included have been designed to be easy to respond to and not too lengthy.

At each visit the researcher will go through all completed questionnaires with the patient to ensure that all the questions have been answered and to avoid missing data in the final analysis.

7.1 Sample Size

Weare planning investigate change in sexual function, using the sexual quality of life questionnaire (SQOL_F) and the prolapse and incontinence sexual questionnaire (PISQ_12) as measures of sexual function at baseline and 12 weeks after intervention. Prior data indicates {Roger R 2008} that a difference in the response to SQOL_F (Primary outcome) of matched pairs is normally distributed with standard deviation 19.2 and a difference in the mean response of 6.4. We used these estimates to calculate sample size using 95% power, and two sided alpha level of 0.05. The number of participants required to detect the difference described at the significance level described, would be 120 patients. Allowing for about 10% dropout the number required would be 132.

Rogers R et al (2008) Efficacy of tolterodine on overactive bladder symptoms and sexual and emotional quality of life in sexually active women. Int Urogynaecol J, 19, 11, 1551-7.

7.2 Randomisation

No randomisation will take place in this study. All subjects meeting the entry criteria will receive the study drug.

7.3 Analysis

At week 4 demographics will be compared among those who dose escalate and those who don't to ensure that there are no differences between the two groups. Significance will be at the 5% level. We anticipate that the design of the study will minimise missing data and intention to treat is not applicable in these circumstances.

Wilcoxon Signed Ranks and Students paired t-test will be used to analyse medians and means respectively comparing baseline and week 12 for KHQ, Pac- QoL, SQoL and PISQ-12. Comparisons of the difference in baseline and 12 week PPBC scores will also be analysed. Multivariate linear regression will be used to examine changes in KHQ, Pac-QoL, SQoL and PISQ-12 at week 12.

To assess changes in first sensation to void and maximum cystometric capacity paired T tests will be performed. The time to first contraction will be analysed using a Kaplan Mayer test and compared using a log rank test.

A regression analysis will be performed to assess if change in quality of life scores are related to changes in the urodynamic variables.

9. Trial Steering Committee

This study does not have a trial steering committee. The protocol has been externally peer reviewed by medical consultant with experience in designing and completing CTIMP's.

10 Direct Access to Source Data and Documents

The Investigator(s) will permit trial-related monitoring, audits, REC review, and regulatory inspections (where appropriate) by providing direct access to source data and other documents (ie patients' case sheets, blood test reports, X-ray

reports, histology reports etc).

11 Ethics & Regulatory Approvals

The trial will be conducted in compliance with the principles of the Declaration of Helsinki (1996), the principles of GCP and in accordance with all applicable regulatory requirements including but not limited to the Research Governance Framework and the Medicines for Human Use (Clinical Trial) Regulations 2004, as amended in 2006 and any subsequent amendments.

This protocol and related documents will be submitted for review to a Research Ethics Committee (REC), and to the Medicines and Healthcare products Regulatory Agency (MHRA) for Clinical Trial Authorisation.

Any subsequent protocol amendments will submitted to the REC and Regulatory Authorities for approval, and the study will comply with all regulations including pharmacovigilance reporting.

Annual progress and safety reports and a final report at conclusion of the trial will be submitted to the KHP-CTO (on behalf of the Sponsor), the REC and the MHRA within the timelines defined in the Regulations

12 Quality Assurance

Monitoring of this trial will be to ensure compliance with Good Clinical Practice and scientific integrity will be managed and oversight retained by the King's Health Partners Clinical Trials Office Quality Team.

13 Data Handling

The Chief Investigator will act as custodian for the trial data. The following guidelines will be strictly adhered to:

Patient data will be anonymised.

- All anonymised data will be stored on a password protected computer.
- All trial data will be stored and archived in line with the Medicines for Human Use (Clinical Trials) Amended Regulations 2006 as defined in the King's Health Partners Clinical Trials Office Archiving SOP.

14 Publication Policy

It is intended that the results of the study will be reported and disseminated at international conferences and in peer-reviewed scientific journals.

15 Financial Aspects

Funding to conduct the trial is provided by an Investigator Initiated Research Grant from Pfizer Ltd.

16 Signatures

_____ _____

Chief Investigator Date
Print name

_____ _____

Principal Medical Investigator Date
Print name

Participant Study Number	Protocol Number: 2010-023851-27
VISIT 1 (SCREENING)	**DEMOGRAPHIC DATA**

Participant Informed Consent:			
Date participant signed written consent form:	__ __ / __ __ __ / __ __ __ __ (DD / MMM / YYYY)	**Date of first trial-related procedure:**	__ __ / __ __ __ / __ __ __ __ (DD / MMM / YYYY)

Demographic Data:	
Date of Birth:	__ __ / __ __ __ / __ __ __ __ (DD / MMM / YYYY)
Origin:	☐ White / Caucasian ☐ Black or African ☐ Oriental ☐ Other, specify: _____

Participant Study Number	Protocol Number: 2010-023851-27
VISIT 1 (SCREENING)	**MEDICAL HISTORY**

Has the patient had any relevant medical history?	☐ **No** ☐ **Yes,** Complete below		
Condition / illness /surgical procedure	**Start date** (DD/MMM/YYYY)	**Stop date** (DD/MMM/YYYY)	**Or tick if ongoing at Screening Visit?**
	___/___/___	___/___/___	☐
	___/___/___	___/___/___	☐
	___/___/___	___/___/___	☐
	___/___/___	___/___/___	☐
	___/___/___	___/___/___	☐
	___/___/___	___/___/___	☐
	___/___/___	___/___/___	☐
	___/___/___	___/___/___	☐
	___/___/___	___/___/___	☐
	___/___/___	___/___/___	☐
	___/___/___	___/___/___	☐
	___/___/___	___/___/___	☐

Participant Study Number	Protocol Number: 2010-023851-27
VISIT 1 (SCREENING)	**SCREENING CONCOMITANT MEDICATIONS**

Has the participant taken any concomitant medications at screening or prior to screening?		☐ **No** ☐ **Yes,** Complete below		
Medication (Record <specify Generic or Brand> name)	**Reason for use** (Enter Medical History diagnosis or other reason for use, e.g. Prophylaxis)	**Start Date** (DD/MMM/YYYY)	**Stop Date** (DD/MMM/YYYY)	**Or tick if ongoing at Screening Visit**
1.		___/___/___	___/___/___	☐
2.		___/___/___	___/___/___	☐
3.		___/___/___	___/___/___	☐
4.		___/___/___	___/___/___	☐
5.		___/___/___	___/___/___	☐
6.		___/___/___	___/___/___	☐
7.		___/___/___	___/___/___	☐
8.		___/___/___	___/___/___	☐
9.		___/___/___	___/___/___	☐
10.		___/___/___	___/___/___	☐

Participant Study Number	Protocol Number: 2010-023851-27
VISIT 1 (SCREENING)	**VITAL SIGNS**

Were Vital Signs performed?	☐ **No** ☐ **Yes,** Complete below
Date of Vital Signs: __ __ / __ __ __ / __ __ __ __ (DD / MMM / YYYY)	
Blood Pressure (supine) :	___ ___ ___ / ___ ___ ___ mmHg
Pulse: ___ ___ ___ beats/min	
Weight: ___ ___ ___ . ___ kg	**Height:** ___ . ___ ___ m
BMI: ___ ___	
Urinalysis:	**PVR:** ___ ___
Pregnancy test:	
Menopausal status:	

Participant Study Number			Protocol Number: 2010-023851-27
VISIT 1 (SCREENING)			**PHYSICAL EXAM**

Was Physical Examination performed? ☐ **No** ☐ **Yes, Complete below**				
System	***Abnormal**	**Normal**	**Not done**	***If noted ABNORMAL, please provide brief description**
General Appearance	☐	☐	☐	
Genitalia	☐	☐	☐	
Anorectal	☐	☐	☐	
Neurologic	☐	☐	☐	
Others	☐	☐	☐	

Participant Study Number	Protocol Number: 2010-023851-27
VISIT 1 (SCREENING)	**INCLUSION CRITERIA**

The following criteria MUST be answered YES for participant to be included in the trial (except where NA is appropriate):		**Yes**	**No**	**NA**
1.	Female aged 18 – 80 years.	☐	☐	☐
2.	Overactive bladder symptoms (subject reported) for ≥3 months prior to screening visit according to ICS guidelines	☐	☐	☐
3.	Mean number of Urgency episodes ≥3 per 24 hours as verified by the screening bladder diary prior to baseline / Visit 2	☐	☐	☐
4.	Sexually active	☐	☐	☐
5.	Able and willing to complete the micturition bladder diaries and all trial related questionnaires, comply with scheduled clinic visits and clinical trial procedures	☐	☐	☐
6.	Capable of understanding and having signed the informed consent form after full discussion of the treatment and its risks and benefits	☐	☐	☐
7.	Able to speak, read and write in English.	☐	☐	☐

Participant Study Number	Protocol Number: 2010-023851-27
VISIT 1 (SCREENING)	**EXCLUSION CRITERIA**

	The following criteria MUST be answered NO for the participant to be included in the trial:	**Yes**	**No**
1.	Any condition that would contraindicate the use of fesoterodine including, but not limited to: hyposensitivity to the active substance (fesoterodine fumarate) or any of the excipients, or to peanut, lactose or soya; urinary retention; gastric retention; uncontrolled narrow angle glaucoma; myasthesia gravis; moderate or severe hepatic impairment; severe renal impairment; severe ulcerative colitis; and toxic megacolon.	☐	☐
2.	Stage 3 or greater pelvic organ prolapse, defined as tissue protuding to or beyond the introitus in lithotomy position at rest (without increase in intra abdominal pressure).	☐	☐
3.	History of lower urinary tract surgery (eg. Incontinence surgery, diverticulectomy, OTIS urethrotomy) with the exception of any minor surgery (eg. Cystoscopic procedures).	☐	☐
4.	A known history of interstitial cystitis or a significant pain component associated with OAB symptoms, uninvestigated haematuria, urogenital cancer, interstitial or external radiation to the pelvis or external genitalia, or bladder outlet obstruction, radiation cystitis, genitor-urinary tuberculosis, bladder calculi, urethral obstruction or detrusor-sphincter dysynergia.	☐	☐
5.	Subjects with bladder stones. Subjects with a previous history of bladder stones may be included.	☐	☐
6.	Previous history of acute urinary retention requiring catheterisation, clinically relevant bladder outlet obstruction or severe voiding difficulties in the judgement of the investigator prior to Visit 2 (baseline)	☐	☐
7.	Use of an indwelling or an intermittent self-catheterisation programme	☐	☐
8.	Symptoms of incontinence being predominantly stress urinary incontinence as determined by the investigator	☐	☐
9.	Urinary tract infection (UTI) as shown by the results of the urinalysis at screening or recurrent urinary tract infections (RUTIs) defined as treatment for UTI ≥3 times in the last year	☐	☐
10.	Use of any electrostimulation, bladder training, or pelvic floor exercises (with certified incontinence practitioners) within 4 weeks prior to Visit 1 (Screening)	☐	☐
11.	Treatment with antimuscarinic OAB medication with 2 weeks prior to Visit 2 (baseline), including any preparation containing: darifenacin, oxybutynin, propiverine, tolterodine, fesoterodine, solifenacin and trospium.	☐	☐
12.	Initiation of treatment during the 12 week trial period with: a. Any other drug treatment for OAB b. Any drugs with significant anticholinergic, antispasmodic, parasympathetic, or cholinergic agonistic effects	☐	☐

13.	Intermittent or unstable use of diuretics or alpha blockers, or tricyclic antidepressants, oestrogen therapy and any 5AR inhibitors or initiation of such treatment(s) within 2 weeks prior to Visit 2 (baseline)	☐	☐
14.	Use of potent CYP3A4 inhibitors, such as grapefruit juice, macrolide antibiotics (erythromycin, clarithromycin), immunosuppressants (cyclosporine), azole antifungal agents (ketonazole, itraconazole), protease inhibitors within 3 weeks prior to Visit 2 (baseline), or the expectation to start any during the trial.	☐	☐
15.	Administration of medication capable of inducing hepatic enzyme metabolism or transport (eg rifampicin, carbamazepine, phenytoin, phenobarbital, or St John's Wort) at any point in the study or within the 6 weeks prior to Visit 2 (baseline).	☐	☐
16.	Treatment with potent CYP2D6 inhibitors such as bupropion, cinacalcet, fluoxetine, paroxetine or quinine at any point during the study	☐	☐
17.	Participated in any interventional clinical trial or received an investigational drug within 4 weeks prior to Visit 2	☐	☐
18.	History of alcohol abuse and /or any other drug in the opinion of the investigator	☐	☐
19.	Female subjects who are pregnant, nursing, or who are intending to become pregnant during the trial or within three months after the completion of the trial	☐	☐
20.	Female subjects of childbearing potential who are heterosexually active but not using an adequate form of contraception. Reliable contraception methods defined as hormonal methods of contraception (including oral, patches, injected, implants, IUDs, condom with spermicidal foam/gel/film/cream/suppository, tubal ligation male partner who has had a vasectomy for a least 4 months).	☐	☐
21.	Subjects who have any medical (including known history of major haematological, renal, cardiovascular or hepatic abnormalities) or psychological condition or social circumstances that would impair their ability to participate reliably in the trial, or those who may increase the risk to themselves or others by participating	☐	☐
22.	Has any current malignancy except a.Those ≥5 years ago without recurrence b.Excised basal cell skin carcinoma or squamous cell cancer	☐	☐
23.	Subjects who, in the opinion of the investigator, are not likely to complete the trial for any reason	☐	☐
24.	Subjects with an uncontrolled cardiac arrhythmia or congestive heart failure	☐	☐
If any of the above criteria is answered YES, the participant is NOT eligible for the trial and must not be included in the study. Please list reason(s) for ineligibility for screen failure on Participant Eligibility Review page.			

Participant Study Number	Protocol Number: 2010-023851-27
VISIT 1 (SCREENING)	**PARTICIPANT ELIGIBILITY REVIEW**

End of Screening Visit Checklist:			
		Yes	**No**
1.	**Does the participant satisfy the inclusion and exclusion criteria to date?**	☐	☐
2.	**Have all Screening Visit procedures been completed?**	☐	☐
3.	**Have the Medical History and Concomitant Medication pages been completed?**	☐	☐
4.	**Is the participant still willing to proceed in the trial?**	☐	☐

Participant's eligibility Investigator Sign-Off:	
Is the participant eligible to take part in the Clinical Trial? **Investigator's Signature**: _____ **Date** : __ __ / __ __ __ / __ __ __ __ (DD / MMM / YYYY) **Investigator's Name:** _____	☐ Yes ☐ No, Please give reason for screen failure below
Reason(s) for screen failure:	
1.	
2.	
3.	

Participant Study Number	Protocol Number: 2010-023851-27
VISIT 2	**PARTICIPANT STATUS**

Date of Visit:	__ / ___ / ____ (DD / MMM / YYYY)

Visit Checklist:

		Yes	No
1.	Has the patient completed the bladder diary correctly	☐	☐
2.	Does the patient meet the inclusion / exclusion criteria	☐	☐
3.	Have there been any new Adverse Events? (If yes, please record in Adverse Events Log)	☐	☐
4.	Have there been any changes in Concomitant Medications? (If yes, please record in Concomitant Medications Log)	☐	☐
5.	Has the patient completed the PISQ-12, SQoL, PPBC, KHQ, PAC-QoL and the SAGA questionnaires	☐	☐
6.	Dispense study medication (4mg fesoterodine) Number of tablets dispensed	☐	☐
7.	Dispense 3 day bladder diary	☐	☐

Participant Study Number	Protocol Number: 2010-023851-27
VISIT 3	PARTICIPANT STATUS

Date of Visit: __ __ / __ __ __ / __ __ __ __
(DD / MMM / YYYY)

Visit Checklist:

		Yes	No
1.	**Have there been any new Adverse Events?** (If yes, please record in Adverse Events Log)	☐	☐
2.	**Have there been any changes in Concomitant Medications?** (If yes, please record in Concomitant Medications Log)	☐	☐
3.	**Review Bladder diary?**	☐	☐
4.	**Does the patient want to increase the dose of medication?**	☐	☐
5.	**Has the returned medication been counted and compliance assessed?**	☐	☐
6.	**Dispense bladder diary**	☐	☐
7.	**Dispense study medication** **Number of tablets** **Dose**	☐	☐

Study Drug Compliance

Number of tablets returned **tablets**

Number of tablets taken since last visit (A) **tablets**

Number of days since baseline visit (B)	**days**
Compliance: (A/B x 100)	

Participant Study Number	Protocol Number: 2010-023851-27
VISIT 4	PARTICIPANT STATUS

Date of Visit:	__ __ / __ __ __ / __ __ __ __ (DD / MMM / YYYY)

Visit Checklist:

		Yes	No
1.	Have there been any new Adverse Events? (If yes, please record in Adverse Events Log)	☐	☐
2.	Have there been any changes in Concomitant Medications? (If yes, please record in Concomitant Medications Log)	☐	☐
3.	**Has a pregnancy test been performed?**	☐	☐
4.	**Review bladder diary**	☐	☐
5.	**Has the patient completed the PISQ-12, SQoL, PPBC, KHQ, PAC-QoL and the SAGA questionnaires**	☐	☐
6.	**Count medication returned and assess compliance**	☐	☐

Study Drug Compliance

Number of tablets returned	**tablets**
Number of tablets taken since last visit (A)	**tablets**
Number of days since baseline visit (B)	**days**
Compliance: (A/B x 100)	**%**

Participant Study Number	Protocol Number: 2010-023851-27
VISIT 5 Telephone follow up	PARTICIPANT STATUS

Date of Visit: __ __ / __ __ __ / __ __ __ __
(DD / MMM / YYYY)

Visit Checklist:

		Yes	No
1.	**Have there been any new Adverse Events?** (If yes, please record in Adverse Events Log)	☐	☐
2.	**Has the patient continued on a treatment** **If yes then which?**	☐	☐

Participant Study Number			Protocol Number: 2010-023851-27

CONCOMITANT MEDICATIONS LOG

Has the participant used any Concomitant Medications? ☐ **No** ☐ **Yes,** Complete below

CM No.	Medication name (Record <specify Generic or Brand> name)	Start date (DD/MMM/YYYY)	Stop date (DD/MMM/YYYY)	Or tick if ongoing at end of study?	Reason for use (Enter related AE diagnosis, or other reasons for use, e.g. Prophylaxis)	Dose (Units)	Route	Frequency
1.		___/___/___	___/___/___	☐				
2.		___/___/___	___/___/___	☐				
3.		___/___/___	___/___/___	☐				
4.		___/___/___	___/___/___	☐				
5.		___/___/___	___/___/___	☐				
6.		___/___/___	___/___/___	☐				
7.		___/___/___	___/___/___	☐				
8.		___/___/___	___/___/___	☐				

☐ **Please check box if this is the last page used**

Participant Study Number			Protocol Number: 2010-023851-27

CONCOMITANT MEDICATIONS LOG (CONTINUATION PAGE)

CM No.	Medication name (Record <specify Generic or Brand> name)	Start date (DD/MMM/YYYY)	Stop date (DD/MMM/YYYY)	Or tick if ongoing at end of study?	Reason for use (Enter related AE diagnosis, or other reasons for use, e.g. Prophylaxis)	Dose (Units)	Route	Frequency
__.		___/____/____	___/____/____	☐				
__.		___/____/____	___/____/____	☐				
__.		___/____/____	___/____/____	☐				
__.		___/____/____	___/____/____	☐				
__.		___/____/____	___/____/____	☐				
__.		___/____/____	___/____/____	☐				
__.		___/____/____	___/____/____	☐				
__.		___/____/____	___/____/____	☐				

☐ Please check box if this is the last page used

Participant Study Number	Protocol Number: 2010-023851-27

VISIT _____ ADVERSE EVENTS LOG (CONTINUATION PAGE)

Has the participant experienced any Adverse Events for the duration of the trial? ☐ **No** ☐ **Yes,** Complete below

AE No	Event Name (Please give Diagnosis if known)	Status 1-New AE 2- Ongoing AE no change** 3- Ongoing AE with changes	Start date (DD/MMM/YYYY)	Stop date (DD/MMM/YYYY)	Serious? If serious, please completed a JCTO SAE form	Con-comitant Medication given	Intensity 0 - Mild 1 - Moderate 2 - Severe	Study Drug Action 0 - None 1 - Temporarily Interrupted 2 - permanently withdrawn	Outcome 0 - Resolved 1- Resolved with sequele 2 - Not resolved	Relationship to Study Drug 0 - Unlikely 1 – Possibly 2 – Likely 3 - Definitely
—			___/___/___	___/___/___	☐ No ☐ Yes	☐ No ☐ Yes				
—			___/___/___	___/___/___	☐ No ☐ Yes	☐ No ☐ Yes				
—			___/___/___	___/___/___	☐ No ☐ Yes	☐ No ☐ Yes				
—			___/___/___	___/___/___	☐ No ☐ Yes	☐ No ☐ Yes				
—			___/___/___	___/___/___	☐ No ☐ Yes	☐ No ☐ Yes				
—			___/___/___	___/___/___	☐ No ☐ Yes	☐ No ☐ Yes				

☐ Please check box if this is the last pag

Participant Study Number	Protocol Number: 2010-023851-27

VISIT _____ ADVERSE EVENTS LOG (CONTINUATION PAGE)

Has the participant experienced any Adverse Events for the duration of the trial? ☐ **No** ☐ **Yes,** Complete below

AE No	Event Name (Please give Diagnosis if known)	Status 1-New AE 2- Ongoing AE no change** 3- Ongoing AE with changes	Start date (DD/MMM/YYYY)	Stop date (DD/MMM/YYYY)	Serious? If serious, please completed a JCTO SAE form	Con-comitant Medication given	Intensity 0 - Mild 1 - Moderate 2 - Severe	Study Drug Action 0 - None 1 - Temporarily Interrupted 2 - permanently withdrawn	Outcome 0 - Resolved 1- Resolved with sequele 2 - Not resolved	Relationship to Study Drug 0 - Unlikely 1 – Possibly 2 – Likely 3 - Definitely
__			___/___/___	___/___/___	☐ No ☐ Yes	☐ No ☐ Yes				
__			___/___/___	___/___/___	☐ No ☐ Yes	☐ No ☐ Yes				
__			___/___/___	___/___/___	☐ No ☐ Yes	☐ No ☐ Yes				
__			___/___/___	___/___/___	☐ No ☐ Yes	☐ No ☐ Yes				
__			___/___/___	___/___/___	☐ No ☐ Yes	☐ No ☐ Yes				
__			___/___/___	___/___/___	☐ No ☐ Yes	☐ No ☐ Yes				

☐ Please check box if this is the last pag

Participant Study Number	Protocol Number: 2010-023851-27

TRIAL COMPLETION

Did participant complete the trial?	☐ **Yes,** Please provide **date of last visit**: __ __ /_____/ 2 0__ __ (DD / MMM / YYYY) ☐ **No,** Please provide **date of withdrawal** and complete below: __ __ /_____/ 2 0__ __ (DD / MMM / YYYY)

<u>Early Withdrawal:</u> please tick most appropriate reason for participant not completing the trial:

☐ **Adverse Events related:** please state related AE: _____

☐ **Participant's decision, specify:** _____

☐ **Investigator's decision, specify:** _____

☐ **Sponsor's decision**

☐ **Lost to follow up**

☐ **Other, specify:** _____

Participant Study Number	Protocol Number: **2010-023851-27**

PRINCIPAL INVESTIGATOR'S SIGN OFF

Principal Investigator's Signature Statement:

I have reviewed this CRF and confirm that, to the best of my knowledge, it accurately reflects the study information obtained for this participant. All entries were made either by myself or by a person under my supervision who has signed the Delegation and Signature Log.

Principal Investigator's Signature:

_____

Principal Investigator's Name:

_____

Date of Signature: ____/_____/_____
(DD / MMM / YYYY)

ONCE SIGNED, NO FURTHER CHANGES CAN BE MADE TO THIS CRF WITHOUT A SIGNED DATA QUERY FORM.

King's College Hospital NHS
NHS Foundation Trust

Patient Information Sheet

1. Introduction

You are being invited to take part in a study. Before you decide to take part, it is important for you to understand why this research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

2. What is the purpose of the study?

You are being asked to take part in a research drug study because you have symptoms which include having to pass urine frequently (and sometimes a desire to pass urine which is difficult to control). You may also have incontinence (the accidental loss of urine). Your doctor has concluded that your symptoms are most likely due to an overactive bladder (OAB).

The study will involve the drug fesoterodine fumarate (from now on referred to as fesoterodine), which is a drug already licensed and routinely used in the UK for this condition.

The study aims to assess whether this drug improves sexual function in women with overactive bladder. In addition it also aims to demonstrate if the drug reduces the amount of times patients need to pass urine. It will also assess how well tolerated fesoterodine is and look at how many women feel they need to change the dose of the medication to best manage their symptoms.

3. Why have I been chosen?

You have been identified as potentially meeting the eligibility criteria for this trial. We are looking to recruit 130 women from our clinics to participate in this study.

4. Do I have to take part?

It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and given time to review the information.

If you decide not to take part, you do not have to give a reason. If you decide to take part you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive. If you decide to withdraw, any data (information) collected up to the point you withdraw may be used in order to preserve the value of the study, however no further information will be collected.

5. What will happen to me if I take part?

If you decide to take part in this study, your involvement will last approximately 12 weeks. You will be asked to visit your study doctor or nurse initially to determine eligibility, and then return for a further three (3) visits for study drug and assessments. You may also have further bladder function tests performed at the end of the study if you are one of the first forty patients who enter the study.

You will be required to sign an informed consent form once all the study information has been clearly explained to you, including the risks and benefits of taking part and any procedures and tests to be performed and you have been given enough time to consider whether you wish to take part in this study. Your study doctor will be available to answer any questions you may have and will also sign the consent form. You will be given a copy of the information sheet and consent form for your records.

If you agree to take part in this study, after signing the informed consent form the following tests will be carried out to determine whether you are eligible to take part in this study. These tests / procedures are called "screening" procedures:

Visit 1 (Screening visit)

At your screening visit:

- Your weight, medical history (including any medication and non-drug treatment) and demography will be taken.
- Your sitting blood pressure and pulse will be taken
- A physical examination will be conducted.
- You will need to provide a sample of your urine for the following-:
    - A urine dipstick test will be performed on a sample of urine to exclude blood and infection
    - A urine pregnancy test for women of child bearing potential will be performed
- You will be issued with a 3-day bladder diary to complete and provided with instructions on how and when to complete the diary. The diary is provided for you to record details of the number of times you pass urine and related information and the completed diary will be collected at your next visit. The diary should be completed for the three (3) days prior to your next visit.
- You will be provided with a questionnaire to help identify and help the study team understand what you would like to achieve in regards to your bladder conditions. You will also be provided with instructions on how to complete the questionnaire. You will be able to review this at home and either complete this at home or complete it at your next visit.

If you meet all of the study entry requirements and you agree to participate in the study, the clinic/research staff will ask you to return for Visit 2 (baseline visit).

Visit 2 (Week 0) (Baseline)

At this visit you will be told if you are still eligible to take part in this study. If you are eligible and still wish to participate, the next step is for you to have the baseline visit.

At the baseline visit-:

- Your completed bladder diary will be collected and evaluated
- You will be asked to complete 6 questionnaires which will take approximately 30 minutes in total
- You will be asked if you have had any new symptoms or worsening of existing symptoms and if you have taken any new medication or treatments since your last visit.
- You will be given another 3-day diary (plus instructions) to complete the three days prior to the next visit (visit 3). The completed diary will be collected at your next visit.
- You will be given a supply of study medication (fesoterodine 4mg) to take once a day at approximately the same time each day over the next 4 weeks. You should take your study medication with water and it should be swallowed whole without chewing. Your study medication can be taken with or without food.

Visit 3 (Week 4)

Four (4) weeks later you will return for visit 3. During this visit:

- Your completed bladder diary will be collected and evaluated.
- You will be asked if you have had any new symptoms or worsening of existing symptoms and if you have taken any new medication or treatments since your last visit.
- Your study doctor will review the amount of unused study medication you have returned to assess whether this has been taken correctly.
- You will be given another 3-day diary (plus instructions) to complete the three days prior to the next visit (visit 4). The completed diary will be collected at your next visit.
- Your dose of study medication will be reviewed by the study doctor and if applicable your dose maybe increased
- You will be given a supply of study medication either fesoterodine 4 mg or fesoterodine 8 mg depending on discussions with your study doctor. You will need to take this once a day at approximately the same time each day over the next 8 weeks.

Visit 4 (Week 12 End of Treatment or Early Termination Visit)

Eight (8) weeks later you will return for visit 4. During this visit:

- Your completed bladder diary will be collected and evaluated
- Women of child bearing potential will need to provide a sample of urine for a pregnancy test

- You will be asked to complete questionnaires which will take approximately 30 minutes
- You will be asked if you have had any new symptoms or worsening of existing symptoms and if you have taken any new medication or treatments since your last visit.
- Your study doctor will review the amount of unused study medication you have returned to assess whether this has been taken correctly.
- If you are one of the women having bladder function tests (urodynamics) performed the following will happen at this visit. Two tubes (a catheter and a pressure line) are inserted into the bladder and a pressure line is inserted into the rectum (or vagina). The bladder is then filled with saline. Any changes of pressure in the bladder are recorded during this time. Once the bladder is full the catheter is removed. Patients may be asked to cough to assess for bladder symptoms. Finally patients will urinate into a flowmeter to assess the pressures within their bladder as it empties. The test takes approximately 15 minutes. There is a slight chance that you will experience some discomfort when you urinate for a couple of hours after the test. There is a 1% risk of developing a urinary infection from the test.

Telephone Follow up (Week 24)

Three months after you have completed the trial the team will call you at home. During this conversation:

- You will be asked if you are currently taking any medication for your bladder and if so which one.
- If you have stopped taking any bladder medication you will be asked why
- You will be asked if you have had any new symptoms or worsening of existing treatments since your last visit.

Unplanned Visits

During the course of the study you might have an additional visit for safety related issues. At this visit the following may be performed:

- Your sitting blood pressure and pulse rate will be measured
- You will be asked if you have had any new symptoms or worsening of existing symptoms and if you have taken any new medication or treatments since your last visit.
- Your study doctor will review the amount of unused study medication you have returned to assess whether this has been taken correctly.

What happens to my urine samples?

Any urine samples that you have given will be destroyed immediately after use and will not be used for any other purpose.

Payment

You will be reimbursed for any reasonable extra expenses (such as travel, car parking expenses) needed to take part in this study (up to a maximum of £20 per visit on receipt of valid travel tickets or car parking vouchers).

The payment will be made in the form of a crossed cheque that must be paid into a bank account bearing your name or by cash. You are responsible for paying tax on this payment if this is appropriate to your circumstances.

If you one of the participants asked to have additional urodynamics performed at Visit 4 you will be offered £50 for any discomfort or inconvienience this may cause.

There will be no other payment for participation in the study.

6 What do I have to do?

If you decide to take part in this study you will be asked to:

- Keep all scheduled appointments.
- Take the study medicine exactly the way you are told. Do not stop taking the medicine without first talking to the study doctor.
- Do not give the medicine to anyone else. Keep the medicine out of the reach of children.
- Store the medication according to instructions.
- Do not take any other medicines for overactive bladder and/or incontinence
- Tell your study doctor about any medications that you take, even if it is medicine you buy without a prescription or is a herbal remedy.
- Notify your study doctor if you are allergic to peanuts or soya.
- Notify your study doctor if you eat or drink grapefruit.
- Tell your study doctor about any side effect, injury, symptom or complaint you experience, by using the contact numbers at the end of this patient information sheet.
- If applicable, avoid becoming pregnant, breast feeding while on the study and for 28 days after your last dose of fesoterodine by using suitable contraception approved by your study doctor. You should not breast feed whilst you are in the study
- Return the unused study drug and containers to the study doctor at scheduled visits.

- You will be provided with a card, which says that you are taking part in this study. Carry this card with you at all times, and show it to any doctors, nurses or pharmacists. Please return the card at the end of the study.
- Complete the diary for the three days prior to your visit 2, 3 and 4.

7 What is the drug or procedure that is being tested?

The drug being studied is called fesoterodine which helps to relax the bladder. It was developed for the treatment of overactive bladder with symptoms of urgency urinary incontinence, urgency, and urinary frequency.

In May 2007 it was approved in Europe and in March 2008 it was approved in the UK. The fesoterodine Prolonged Release tablet is suitable for once-daily administration.

For the first four weeks of drug treatment in this study you will take one tablet of fesoterodine 4 mg at approximately the same time every day. After the first four weeks following on from discussions with your study doctor you will either take one 4mg tablet or be increased up to take one 8 mg tablet, at approximately the same time every day, for the duration of the study.

8. What are the alternatives for diagnosis or treatment?

You do not have to be in this study to receive treatment for your overactive bladder. There may be other ways to treat your condition including-:

- Other already approved medications, which could include fesoterodine, as recommended by your regular doctor
- The use of behavioral techniques that can improve bladder control
- Surgical interventions to control overactive bladder symptoms

Your study doctor can tell you more about these other treatments and their benefits and risks.

9 What are the side effects of any treatment received when taking part?

As with all studies, the drug treatment and other therapies may involve risks that are already known as well as risks that are currently unknown. Based on studies and the experience of other people who have received fesoterodine some side effects may occur. If any information on new risks or side effects becomes available during the course of the study then you will be informed. This information may affect your decision about continuing in the study.

Very common side effects (occurring in 10% of patients)

- You may get a dry mouth. This effect is usually mild or moderate.

Common side effects (occurring in 1-10% of patients)

- Dry eye
- Stomach ache
- Constipation
- Diarrhoea
- Trouble digesting food (dyspepsia)
- Feeling sick (nausea)
- Pain or discomfort when emptying the bladder (dysuria)
- Difficulty in sleeping (insomnia)
- Dry throat
- Dizziness
- Headache

You should use caution in driving, operating machinery, or doing other dangerous activities until you know how fesoterodine affects you. Blurred vision and drowsiness are possible side effects of medicines such as fesoterodine.

Most of the people who have experienced these side effects considered them to be mild or moderate, and most of them decided to continue treatment despite the side effects.

However if you suffer from any of these side effects listed, or you notice any which are not listed here please report these as soon as they occur whether or not you think that they are linked to the study drug.

Finally, other side effects that are not known at this time could occur during your treatment.

If you do experience any side effects or discomfort during the study you should inform your study doctor either at the next visit or sooner if you wish by using the telephone contact number at the end of this information sheet. Your study doctor will advise you what to do.

10. What are the possible disadvantages and risks of taking part?

There could be risks to an unborn child in this study. If you are pregnant or may become pregnant during the study, these risks could affect you or your unborn child. Unless you have been surgically sterilised (you have had your womb and/or ovaries removed) or are postmenopausal you must agree to use birth control during the study. Your study doctor must approve the form of birth control. Acceptable contraceptive methods:

- Hormonal methods of contraception (including oral, patches, injected, implants, IUDs (intrauterine device)) at least 14 days prior to the first dose of trial medication;
- Placement of a copper-containing intrauterine device (IUD);

- Condom with spermicidal foam/gel/film/cream/suppository
- Tubal ligation
- Male partner who has had a vasectomy for at least 4 months ~~e.~~f. Abstinence

If you are abstinent but become sexually active at any time during the study, you should use one of the contraceptive methods above.
If you could become pregnant, you will have a pregnancy test at the beginning of the study to ensure that you are not pregnant. You will also have another test at the end of the study. This test might not detect an early pregnancy. Pregnancy tests may be repeated during the study. If you think you are pregnant, tell the study doctor immediately.

Pregnancy will be a reason to stop study treatment. If you become pregnant during the study, you may be discontinued from study participation for safety reasons. In either case, please make your obstetrician aware of your study participation. Your study doctor will ask that you, or your obstetrician, provide updates on the progress of your pregnancy and its outcome. The study doctor will make this information available to the sponsor for safety monitoring follow- up.

You will not be able to take part in this study if you are breast-feeding.

There is a possibility that fesoterodine might not work for you or might not work as well as another medicine.

If you have private life/medical insurance please check with the insurance company, before agreeing to take part in this study, to ensure that your participation will not affect your cover.

11. What are the possible benefits of taking part?
The medicine you receive may help relieve your symptoms of your overactive bladder, but this cannot be guaranteed and you may not receive any direct benefit from taking part in this study.

The information we gain from this study might help us to treat future patients with overactive bladder.

12 What if new information becomes available?
Sometimes during the course of a study, important new information becomes available about the drug that is being studied. If this happens, your study doctor will tell you about it and discuss with you whether you want to continue in the study. If you decide to withdraw your study doctor will make arrangements for your care to continue. If you decide to continue in the

study you will be asked to sign an updated informed consent form which includes the new information and will be given a copy of this form to keep.

Also, on receiving new information your study doctor might consider it to be in your best interests to withdraw you from the study. He/she will explain the reasons why it is best that you do not continue on study and will arrange for your ongoing medical care.

13 What happens when the study stops?

At the end of the study you will no longer receive fesoterodine as part of the clinical trial. It is unlikely that fesoterodine would be available to you in the community. Your study doctor or nurse will assess your symptoms and suggest alternative medications which your GP can continue to prescribe for you.

As with any study, there is a possibility that this study could close early due to various reasons such as no beneficial effect, unacceptable side effects being reported or unexpected reasons. If at any time during the study you develop an illness or condition, which in the opinion of the study doctor makes it unsafe for you to continue, you will be withdrawn from the study and a final assessment will be made.

14 Removal from the study

Your study doctor or the sponsor may decide to take you out of the study if:

- You do not follow the directions of the study doctor
- You develop a serious illness that is not related to taking part in the study
- Your study doctor decides that the study is not in your best interest
- Regulatory Authorities, or Research Ethics Committee, decide to stop the study
- You become pregnant, intend to become pregnant, or are breast-feeding a child during this study

If you are taken out of the study you may undergo some tests. These include:

- Your completed bladder diary will be collected and evaluated
- Your sitting blood pressure and pulse rate will be measured
- Women of child bearing potential will need to provide a sample of urine for a pregnancy test
- You will be asked to complete 6 questionnaires which will take approximately 30 minutes
- You will be asked if you have had any new symptoms or worsening of existing symptoms and if you have taken any new medication or treatments since your last visit.
- Your study doctor will review the amount of unused study medication you have returned to assess whether this has been taken correctly.

The tests are to protect your safety. The study doctor may also recommend other treatments.

15 Withdrawal from the study

If you decide to withdraw from the study you should tell the study doctor. If you withdraw from the study without telling the study doctor, you may be contacted to confirm whether you have withdrawn or wish to continue your participation in the study. If you do withdraw from the study, no new information about you will be collected by study personnel, although information about you that has already been collected may continue to be used in order to preserve the value of the study. If you have any questions or concerns about this, it is recommended that you contact the study doctor.

16 What if something goes wrong?

We do not expect you to suffer any health problems by taking part in this study.
If taking part in this study harms you, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for a legal action, but you may have to pay for it.
If you wish to complain about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms will be available to you.

17 Will my taking part in this study be kept confidential?

If you join the study, the doctors, nurses and other personnel involved in this study may need access to your medical history, including your past medical records and test results, for the purposes of this study. By signing the consent form you agree that the study personnel can contact your family doctor and other health care providers to gain access to your medical history during this study.

In addition, some parts of your medical records and the data collected will be looked at by monitors, auditors, ethics committees, authorised persons from King's College Hospital NHS Trust (the sponsor of this research), and representatives of regulatory authorities, to check that the study is being carried out correctly.. All will have a duty of confidentiality to you as a research participant. By signing the consent form you agree to this access for the current study.

Any records identifying you will be kept confidential and won't be made publicly available.

With your consent your family doctor (General Practitioner) will be told that you have decided to take part in this study.

18 Your right to access health information

You have a right to ask for access to the health information that the study doctor holds about

you and to ask for changes if your health information if not correct or is incomplete, in accordance with UK law. Any request for access or changes should be made to the study doctor.

19 What will happen to the results of the study?

Once all the study results are available your study doctor will be happy to discuss this with you. A final report will be produced and may be published. A copy of the publication will be available from King's College Hospital on request. Please note that your name will not appear in the final report or publication. This study is part of an educational project.

20 Who is funding the study?

This study is being funded by an Investigator Initiated Research Grant from Pfizer Ltd. Some members of the Urogynaecology team perform consultancy work for Pfizer Ltd.

21 Who has reviewed this study?

The study has been approved by Cambridge East Research Ethics Committee and the Medicines and Healthcare Products Regulatory Agency (MHRA).

22 Contact names and telephone numbers for further information

For any concerns or other questions about this study, or any questions about a study related injury please contact:

Angie Rantell 0203 299 3568

For emergencies only please contact: Katherine Monk Ward 0203 299 3317

For any concerns about your rights as a participant or any complaints please contact the Patient Advice and Liaison Service (PALS). This is a service that offers support, information and assistance to patients, relatives and visitors. They can also provide help and advice if you have a concern or complaint that staff have not been able to resolve for you. The PALS office is located on the ground floor of the Hambleden Wing, near the main entrance on Bessemer Road - staff will be happy to direct you.

Tel: 020 3299 3601
Textphone: 020 3299 1878

Fax: 020 3299 3626
Email: kch-tr.PALS@nhs.net

Before you sign the informed consent form, you should ask questions about anything that you do not understand. The study staff will answer any questions before, during and after the study.

Thank you for taking the time to read this information sheet.

King's College Hospital NHS
NHS Foundation Trust

Centre: King's College Hospital
Patient identification Number for this Study: _____

CONSENT FORM

A 12 week, single centre, open label study to evaluate the effect of Fesoterodine flexible dosing regimen on the sexual function of women with overactive bladder

Name of Researcher: Professor Linda Cardozo, FRCOG and Angie Rantell BSc (Hons) RN.

Please initial box

1. I confirm that I have read and understand the information sheet (version 2.0 dated 24/01/2013) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected ☐

3. I understand that relevant sections of any of my medical notes and data collected during the study may be looked at by responsible representatives of the sponsor or the NHS trust, the ethics committee and regulatory authorities, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records ☐

4. I agree to my GP being informed of my participation in the study ☐

5. I agree to have urodynamics performed at Visit 4 ☐

6. I agree to take part in the above study ☐

Name of Patient	Date	Signature
Name of person taking consent	Date	Signature

Dear Doctor .....

RE: Patient ....

Your patient has agree to participate in a clinical study entitled 'A 12 week, single centre, open label study to evaluate the effect of Fesoterodine flexible dosing regimen on the sexual function of women with overactive bladder'.

The study will last approximately 12 weeks and requires 4 visits and their involvement will include the following procedures:-

- Weight, medical history and demography will be taken
- Blood pressure and pulse will be taken
- Physical examination
- Urine dipstick
- Urine pregnancy test for women of child bearing potential
- Completion of questionnaires
- Completion of bladder diary
- Assessment of adverse events and concomitant medications

During the study your patient will receive Fesoterodine. Known side effects of Fesoterodine include:-

- Dry mouth
- Constipation
- Drowsiness
- Blurred vision
- Urinary retention

Most of the people who have experienced these side effects consider them to be mild to moderate, and most of them decide to continue treatment despite the side effects.

Certain concomitant medications are prohibited, these include:-

- Any drug other than the study drug for overactive bladder
- Any drug with significant anticholinergic or antispasmodic effects
- Moderate or potent CYP3A4 inhibitors

- Any medication capable of inducing hepatic enzyme metabolism or transport

- Intermittent or unstable use of diuretics or alphablockers or tricyclic antidepressants, oestrogen therapy and any 5AR inhibitors. Stable usage/dosage is allowed
- Any investigational drug, medical procedure or dietary supplement

I would appreciate it if you would contact me should your patient need any changes to their medications during the time that they are participating in this study.

I would also appreciate it if you could contact me if your patient reports any adverse events to you.

If you would like to see a copy of the inclusion / exclusion criteria and / or if you know of any reason why your patient should not continue in the study I would be grateful if you could let me know as soon as possible.

If you have any queries, please feel free to contact me on 0203 299 33568 or angela.rantell@nhs.net

Yours Sincerely

Angie Rantell
Senior Urogynaecology Nurse Specialist
King's College Hospital

King's College Hospital NHS
NHS Foundation Trust

INVITE TO PARTICIPATE IN A STUDY

We are inviting you to take part in a study that involves a medication called Fesoterodine. This is a licensed drug that is routinely used in UK to treat patients with an overactive bladder (having to go frequently and urgently to the toilet).

The aim of this study is to assess if this drug improves sexual function as well as improving your bladder symptoms.

We would like you to take part in our study. To be eligible you must be:

- ✓ Female, age 18-80 years old
- ✓ Sexually active
- ✓ Have a strong, sudden urge to go to the toilet

This is a 12 week study. You will only need to attend 4 clinic appointments and you will be reimbursed for any extra expenses such as travel and car parking expenses (maximum £20 per visit)

If you **would** like to be part of the study please leave your name and telephone number on this form and hand it in to the nurse or receptionist during your visit.

Name_____Telephone_____

Alternatively for further information please contact Urogynaecology: Angie Rantell or Sarah Ferdinand on 0203 299 3568 or email: Angela.Rantell@nhs.net or Sarah.Ferdinand@nhs.net

Appendix

Pelvic Organ Prolapse/Urinary Incontinence Sexual Function Questionnaire (PISQ-12)

Instructions: Following are a list of questions about you and your partner's sex life. All information is strictly confidential. Your confidential answers will be used only to help doctors understand what is important to patients about their sex lives. Please check the box that best answers the question for you. While answering the questions, consider your sexuality over the past six months. Thank you for your help.

1. How frequently do you feel sexual desire? This feeling may include wanting to have sex, planning to have sex, feeling frustrated due to lack of sex, etc.
   ☐ Always ☐ Usually ☐ Sometimes ☐ Seldom ☐ Never
2. Do you climax (have an orgasm) when having sexual intercourse with your partner?
   ☐ Always ☐ Usually ☐ Sometimes ☐ Seldom ☐ Never
3. Do you feel sexually excited (turned on) when having sexual activity with your partner?
   ☐ Always ☐ Usually ☐ Sometimes ☐ Seldom ☐ Never
4. How satisfied are you with the variety of sexual activities in you current sex life?
   ☐ Always ☐ Usually ☐ Sometimes ☐ Seldom ☐ Never
5. Do you feel pain during sexual intercourse?
   ☐ Always ☐ Usually ☐ Sometimes ☐ Seldom ☐ Never
6. Are you incontinent of urine (leak urine) with sexual activity?
   ☐ Always ☐ Usually ☐ Sometimes ☐ Seldom ☐ Never
7. Does fear of incontinence (either stool or urine) restrict your sexual activity?
   ☐ Always ☐ Usually ☐ Sometimes ☐ Seldom ☐ Never
8. Do you avoid sexual intercourse because of bulging in the vagina (either the bladder, rectum or vagina falling out?)?
   ☐ Always ☐ Usually ☐ Sometimes ☐ Seldom ☐ Never
9. When you have sex with your partner, do you have negative emotional reactions such as fear, disgust, shame or guilt?
   ☐ Always ☐ Usually ☐ Sometimes ☐ Seldom ☐ Never
10. Does your partner have a problem with erections that affects your sexual activity?
    ☐ Always ☐ Usually ☐ Sometimes ☐ Seldom ☐ Never
11. Does your partner have a problem with premature ejaculation that affects your sexual activity?
    ☐ Always ☐ Usually ☐ Sometimes ☐ Seldom ☐ Never

12. Compared to orgasms you have had in the past, how intense are the orgasms you have had in the past six months?
    ☐ Much less intense ☐ Less intense ☐ Same intensity ☐ More intense ☐ Much more intense

Scoring:

Scores are calculated by totaling the scores for each question with 0=never, 4=always. Reverse scoring is used for items 1,2,3 and 4. The short form questionnaire can be used with up to two missing responses. To handle missing values the sum is calculated by multiplying the number of items by the mean of the answered items. If there are more than two missing responses, the short form no longer accurately predicts long form scores. Short form scores can only be reported as total or on an item basis. Although the short form reflects the content of the three factors in the long form, it is not possible to analyze data at the factor level. To compare long and short form scores multiply the short form score by 2.58 (12/31).

Sexual Quality of Life Questionnaire-Female (SQoL-F)

This questionnaire consists of a set of statements, each asking about thoughts and feelings that you may have about your sex life. The statement may be positive or negative.

You are asked to rate <u>each</u> one according to how much you agree or disagree with the statement by circling <u>one</u> of six response choices.

In answering these items the following definitions apply:

<u>Sex life</u>: is both the physical sexual activities and the emotional sexual relationship that you have with your partner.

<u>Sexual activity</u>: Includes any activity which may result in sexual stimulation or sexual pleasure such as intercourse, caressing, foreplay, masturbation (self masturbation or your partner masturbating you) and oral sex (your partner giving you oral sex).

Usually, the first answer that comes into your head is the best one so please do not spend too long on each question.

All your answers will be completely confidential

SQoL-F version 5: 29/10/99

f:\institut\cultadap\project\pf1426\question\usenglish\sqfusaq.doc-1/12/2000

1. When I think about my sex life, it is an enjoyable part of my overall life	*completely agree*	*moderately agree*	*slightly agree*	*slightly disagree*	*moderately disagree*	*completely disagree*
2. When I think about my sex life, I feel frustrated	*completely agree*	*moderately agree*	*slightly agree*	*slightly disagree*	*moderately disagree*	*completely disagree*
3. When I think about my sex life, I feel depressed	*completely agree*	*moderately agree*	*slightly agree*	*slightly disagree*	*moderately disagree*	*completely disagree*
4. When I think about my sex life, I feel like less of a woman	*completely agree*	*moderately agree*	*slightly agree*	*slightly disagree*	*moderately disagree*	*completely disagree*
5. When I think about my sex life, I feel good about myself	*completely agree*	*moderately agree*	*slightly agree*	*slightly disagree*	*moderately disagree*	*completely disagree*
6. I have lost confidence in myself as a sexual partner	*completely agree*	*moderately agree*	*slightly agree*	*slightly disagree*	*moderately disagree*	*completely disagree*
7. When I think about my sex life, I feel anxious	*completely agree*	*moderately agree*	*slightly agree*	*slightly disagree*	*moderately disagree*	*completely disagree*
8. When I think about my sex life, I feel angry	*completely agree*	*moderately agree*	*slightly agree*	*slightly disagree*	*moderately disagree*	*completely disagree*
9. When I think about my sex life, I feel close to my partner	*completely agree*	*moderately agree*	*slightly agree*	*slightly disagree*	*moderately disagree*	*completely disagree*
10. I worry about the future of my sex life	*completely agree*	*moderately agree*	*slightly agree*	*slightly disagree*	*moderately disagree*	*completely disagree*
11. I have lost pleasure in sexual activity	*completely agree*	*moderately agree*	*slightly agree*	*slightly disagree*	*moderately disagree*	*completely disagree*
12. When I think about my sex life, I feel embarrassed	*completely agree*	*moderately agree*	*slightly agree*	*slightly disagree*	*moderately disagree*	*completely disagree*
13. When I think about my sex life, I feel that I can talk to my partner about sexual matters	*completely agree*	*moderately agree*	*slightly agree*	*slightly disagree*	*moderately disagree*	*completely disagree*
14. I try to avoid sexual activity	*completely agree*	*moderately agree*	*slightly agree*	*slightly disagree*	*moderately disagree*	*completely disagree*
15. When I think about my sex life, I feel guilty	*completely agree*	*moderately agree*	*slightly agree*	*slightly disagree*	*moderately disagree*	*completely disagree*
16. When I think about my sex life, I worry that my partner feels hurt or rejected	*completely agree*	*moderately agree*	*slightly agree*	*slightly disagree*	*moderately disagree*	*completely disagree*
17. When I think about my sex life, I feel like I have lost something	*completely agree*	*moderately agree*	*slightly agree*	*slightly disagree*	*moderately disagree*	*completely disagree*
18. When I think about my sex life, I am satisfied with the frequency of sexual activity	*completely agree*	*moderately agree*	*slightly agree*	*slightly disagree*	*moderately disagree*	*completely disagree*

Patient Perception of Bladder Condition (PPBC)

Which of the following statements describes your bladder condition best at the moment?
Please tick ONE box only.

My bladder does not cause me any problems at all	
My bladder causes me some very minor problems	
My bladder causes me minor problems	
My bladder causes me moderate problems	
My bladder causes me severe problems	
My bladder causes me many severe problems	

THE KING'S HEALTH QUESTIONNAIRE

1. How would you describe your health at the present?

Please tick one answer

Very good	⬭
Good	⬭
Fair	⬭
Poor	⬭
Very poor	⬭

2. How much do you think your bladder problem affects your life?

Please tick one answer

Not at all	⬭
A little	⬭
Moderately	⬭
A lot	⬭

Please turn the page

Below are some daily activities that can be affected by bladder problems. How much does your bladder problem affect you?

We would like you to answer every question. Simply tick the box that applies to you

3. ROLE LIMITATIONS	**1 Not at all**	**2 Slightly**	**3 Moderately**	**4 A lot**
A. Does your bladder problem affect your household tasks? (cleaning, shopping etc)	⬭	⬭	⬭	⬭
B. Does your bladder problem affect your job, or your normal daily activities outside the home?	⬭	⬭	⬭	⬭

4. PHYSICAL/SOCIAL LIMITATION	**1 Not at all**	**2 Slightly**	**3 Moderately**	**4 A lot**
A Does your bladder problem affect your physical activities (e.g. going for a walk, running, sport, gym etc)?	⬭	⬭	⬭	⬭
B. Does your bladder problem affect your ability to travel?	⬭	⬭	⬭	⬭
C. Does your bladder problem limit your social life?	⬭	⬭	⬭	⬭
D. Does your bladder problem limit your ability to see and visit friends?	⬭	⬭	⬭	⬭

5. PERSONAL RELATIONSHIPS	**0 Not Applicable**	**1 Not at all**	**2 Slightly**	**3 Moderately**	**4 A lot**
A. Does your bladder problem affect your relationship with your partner?	⬭	⬭	⬭	⬭	⬭
B. Does your bladder problem affect your sex life?	⬭	⬭	⬭	⬭	⬭
C. Does your bladder problem affect your family life?	⬭	⬭	⬭	⬭	⬭

6. EMOTIONS	**1 Not at all**	**2 Slightly**	**3 Moderately**	**4 Very much**
A. Does your bladder problem make you feel depressed?	⬭	⬭	⬭	⬭
B. Does your bladder problem make you feel anxious or nervous?	⬭	⬭	⬭	⬭
C. Does your bladder problem make you feel bad about yourself?	⬭	⬭	⬭	⬭

7.SLEEP/ENERGY	**1 Never**	**2 Sometimes**	**3 Often**	**4 All the time**
A. Does your bladder problem affect your sleep?	⬭	⬭	⬭	⬭
B. Does your bladder problem make you feel worn out and tired ?	⬭	⬭	⬭	⬭

8.Do you do any of the following?	**If so how much?**			
	1 Never	**2 Sometimes**	**3 Often**	**4 All the time**
A. Wear pads to keep dry?	⬭	⬭	⬭	⬭
B. Be careful how much fluid you drink ?	⬭	⬭	⬭	⬭
C. Change your underclothes because they get wet?	⬭	⬭	⬭	⬭
D. Worry in case you smell?	⬭	⬭	⬭	⬭

We would like to know what your bladder problems are and how much they affect you ? From the list below choose only those problems that you have at present. Leave out those that don't apply to you.

How much do they affect you?

FREQUENCY: going to the toilet very often

1. A little	2.Moderately	3. A lot
⬭	⬭	⬭

NOCTURIA: getting up at night to pass urine

1. A little	2.Moderately	3. A lot
⬭	⬭	⬭

URGENCY: a strong and difficult to control desire to pass urine

1. A little	2.Moderately	3. A lot
⬭	⬭	⬭

URGE INCONTINENCE: urinary leakage associated with a strong desire to pass urine

1. A little	2.Moderately	3. A lot
⬭	⬭	⬭

STRESS INCONTINENCE: urinary leakage with physical activity eg. coughing, running

1. A little	2.Moderately	3. A lot
⬭	⬭	⬭

NOCTURNAL ENURESIS: wetting the bed at night

1. A little	2.Moderately	3. A lot
⬭	⬭	⬭

INTERCOURSE INCONTINENCE: urinary leakage with sexual intercourse

1. A little	2.Moderately	3. A lot
⬭	⬭	⬭

WATERWORKS INFECTIONS

1. A little	2.Moderately	3. A lot
⬭	⬭	⬭

BLADDER PAIN

1. A little	2.Moderately	3. A lot
⬭	⬭	⬭

Thank You For Your Time

PAC-QOL ©

PATIENT ASSESSMENT OF CONSTIPATION ©

The following questions are designed to measure the impact constipation has had on your daily life **during the past 2 weeks**. For each question, please tick one box.

The following questions ask you about the <u>intensity</u> of your symptoms. To what extent, during the past 2 weeks...	**Not at all 0**	**A little bit 1**	**Moderately 2**	**Quite a bit 3**	**Extremely 4**
1. have you felt bloated to the point of bursting?	☐	☐	☐	☐	☐
2. have you felt heavy because of your constipation?	☐	☐	☐	☐	☐

The next few questions ask you about the effects of constipation on your <u>daily life</u>. How much of the time, during the past 2 weeks...	**None of the time 0**	**A little of the time 1**	**Some of the time 2**	**Most of the time 3**	**All of the time 4**
3. have you felt any physical discomfort?	☐	☐	☐	☐	☐
4. have you felt the need to open your bowel but not been able to?	☐	☐	☐	☐	☐
5. have you been embarrassed to be with other people?	☐	☐	☐	☐	☐
6. have you been eating less and less because of not being able to have bowel movements?	☐	☐	☐	☐	☐

The next few questions ask you about the effects of constipation on your daily life. To what extent, during the past 2 weeks...	**Not at all 0**	**A little bit 1**	**Moderately 2**	**Quite a bit 3**	**Extremely 4**
7. have you had to be careful about what you eat?	☐	☐	☐	☐	☐
8. have you had a decreased appetite?	☐	☐	☐	☐	☐
9. have you been worried about not being able to choose what you eat (for example, at friend's)?	☐	☐	☐	☐	☐
10. have you been embarrassed about staying in the toilet for so long when you were away from home?	☐	☐	☐	☐	☐
11. have you been embarrassed about having to go to the toilet so often when you were away from home?	☐	☐	☐	☐	☐
12. have you been worried about having to change your daily routine (for example, travelling, being away from home)?	☐	☐	☐	☐	☐

The next few questions ask you about your feelings. How much of the time, during the past 2 weeks...	**None of the time 0**	**A little of the time 1**	**Some of the time 2**	**Most of the time 3**	**All of the time 4**
13. have you felt irritable because of your condition?	☐	☐	☐	☐	☐
14. have you been upset by your condition?	☐	☐	☐	☐	☐
15. have you felt obsessed by your condition?	☐	☐	☐	☐	☐
16. have you felt stressed by your condition?	☐	☐	☐	☐	☐
17. have you been less self-confident because of your condition?	☐	☐	☐	☐	☐
18. have you felt in control of your situation?	☐	☐	☐	☐	☐

The next questions ask you about your <u>feelings</u>. To what extent, during the past 2 weeks...	**Not at all 0**	**A little bit 1**	**Moderately 2**	**Quite a bit 3**	**Extremely 4**
19. have you been worried about not knowing when you are going to be able to open your bowels?	☐	☐	☐	☐	☐
20. have you been worried about not being able to open your bowels when you needed to?	☐	☐	☐	☐	☐
21. have you been more and more bothered by not being able to open your bowels?	☐	☐	☐	☐	☐

The next questions ask about your <u>life with constipation</u>. How much of the time, during the past 2 weeks...	**None of the time 0**	**A little of the time 1**	**Some of the time 2**	**Most of the time 3**	**All of the time 4**
22. have you been afraid that your condition will get worse?	☐	☐	☐	☐	☐
23. have you felt that your body was not working properly?	☐	☐	☐	☐	☐
24. have you had fewer bowel movements than you would like?	☐	☐	☐	☐	☐

The next questions ask you about <u>how satisfied</u> you are. To what extent, during the past 2 weeks...	**Not at all 0**	**A little bit 1**	**Moderately 2**	**Quite a bit 3**	**Extremely 4**
25. have you been satisfied with how often you open your bowels?	☐	☐	☐	☐	☐
26. have you been satisfied with the regularity with which you open your bowels?	☐	☐	☐	☐	☐
27. have you been satisfied with your bowel function?	☐	☐	☐	☐	☐
28. have you been satisfied with your treatment?	☐	☐	☐	☐	☐

SELF ASSESSMENT GOAL ACHIEVEMENT QUESTIONNAIRE (SAGA)

Protocol No: Subject ID:

Visit No: Date (dd-MMM-yyyy)

Not Done:

- The questionnaire is designed to help us understand the goals men and women have for their bladder conditions while on treatment
- In this questionnaire, the term “goal” refers to something you would like to achieve in regards to your bladder conditions. A goal is something that is observable and measurable
- In this questionnaire, the expression “treatment goal” refers to the goals you may have for your badder conditions, for example, reducing the number of times you urinate throughout the day, reducing the sudden need to rush to urinate, reducing when you experience urine loss or leakage, reducing the number of times you get up at night to go to urinate or reducing the sensation of pain or pressure in your lower abdomen.
- **Please read each questions carefully and answer as best as you can and without help from anyone**
- **There are no wrong answers**
- **The information you provide will be discussed with your physician to better understand the goals you have regarding your treatment for your bladder problems**

SELF ASSESSMENT GOAL ACHIEVEMENT QUESTIONNAIRE (SAGA)

Protocol No: Subject ID:

Visit No: Date (dd-MMM-yyyy)

FIRST ASSESSMENT

This is a list of treatment goals related to symptoms that people with bladder conditions commonly experience. Please review the list and indicate how important it is for you to achieve each goal. Please tick only **ONE** box for each question.

	Not Very Important Goal 1	2	3	4	Very Important Goal 5	Not Applicable 0
1. Reduce the number times I go to the toile throughout the day	☐	☐	☐	☐	☐	☐
2. Reduce the number of times I get up at night to go to the toilet	☐	☐	☐	☐	☐	☐
3. Reduce the sensation of pressure in my lower abdomen	☐	☐	☐	☐	☐	☐
4. Reduce the sensation of pressure that prompts me to go to the toilet	☐	☐	☐	☐	☐	☐
5. Reduce the difficulties I have completely emptying my bladder	☐	☐	☐	☐	☐	☐
6. Reduce the difficulty starting or maintaining a urinary stream	☐	☐	☐	☐	☐	☐
7. Reduce the urine loss when I cough, laugh, exercise or sneeze	☐	☐	☐	☐	☐	☐
8. Reduce my urine leakage	☐	☐	☐	☐	☐	☐
9. Reduce the sudden need to rush to the toilet	☐	☐	☐	☐	☐	☐

SELF ASSESSMENT GOAL ACHIEVEMENT QUESTIONNAIRE (SAGA)

Protocol No: Subject ID:

Visit No: Date (dd-MMM-yyyy)

FIRST ASSESSMENT

People have treatment goals for their bladder conditions (for example, improve weak stream, be able to watch a movie from beginning to end without having to go to the toilet, reduce pain while urinating). Please list (up to five) treatment goals you have for your bladder condition and indicate how important it is for you to achieve each goal. Please tick only **ONE** box for each question.

	Not Very Important Goal 1	2	3	4	Very Important Goal 5
10.	☐	☐	☐	☐	☐
11.	☐	☐	☐	☐	☐
12.	☐	☐	☐	☐	☐
13.	☐	☐	☐	☐	☐
14.	☐	☐	☐	☐	☐

SELF ASSESSMENT GOAL ACHIEVEMENT QUESTIONNAIRE (SAGA)

Protocol No: Subject ID:

Visit No: Date (dd-MMM-yyyy)

FIRST ASSESSMENT

Please review the goals that are listed on pages 2 and 3. List the top five goals that you want to achieve the most. In the “Goal No” column, please indicate the number of the goal you are referring to (Nunber 1-14). In the “Success Criteria” column please indicate how and when you would consider this goal achieved.

Ranking	Goal No	Success Criteria
Eg. For most important goal	Goal No 1	Today I urinate on average 15 times a day, I would like to urinate 10 times
Most Important Goal		
Second Most Important Goal		
Third Most Important Goal		
Fourth most Important Goal		
Fifth Most Important Goal		

SELF ASSESSMENT GOAL ACHIEVEMENT QUESTIONNAIRE (SAGA)

Protocol No: Subject ID:

Visit No: Date (dd-MMM-yyyy)

Not Done:

- The questionnaire is designed to help us understand the goals men and women have for their bladder conditions while on treatment
- In this questionnaire, the term “goal” refers to something you would like to achieve in regards to your bladder conditions. A goal is something that is observable and measurable
- In this questionnaire, the expression “treatment goal” refers to the goals you may have for your badder conditions, for example, reducing the number of times you urinate throughout the day, reducing the sudden need to rush to urinate, reducing when you experience urine loss or leakage, reducing the number of times you get up at night to go to urinate or reducing the sensation of pain or pressure in your lower abdomen.
- **Please read each questions carefully and answer as best as you can and without help from anyone**
- **There are no wrong answers**
- **The information you provide will be discussed with your physician to better understand the goals you have regarding your treatment for your bladder problems**

SELF ASSESSMENT GOAL ACHIEVEMENT QUESTIONNAIRE (SAGA)

Protocol No: Subject ID:

Visit No: Date (dd-MMM-yyyy)

FOLLOW-UP ASSESSMENT

Below is a list of symptom goals that people with bladder conditions commonly experience. At your last visit you indicated how important each of these goals was to you. Since your last visit, please indicate to what extent you feel you have achieved each goal. Please tick only **ONE** box for each question.

	Did not achieve goal	Somewhat achieved goal	Achieved Goal	Exceeded Goal	Greatly Exceeded Goal	Not Applicable
1. Reduce the number times I go to the toile throughout the day	☐	☐	☐	☐	☐	☐
2. Reduce the number of times I get up at night to go to the toilet	☐	☐	☐	☐	☐	☐
3. Reduce the sensation of pressure in my lower abdomen	☐	☐	☐	☐	☐	☐
4. Reduce the sensation of pressure that prompts me to go to the toilet	☐	☐	☐	☐	☐	☐
5. Reduce the difficulties I have completely emptying my bladder	☐	☐	☐	☐	☐	☐
6. Reduce the difficulty starting or maintaining a urinary stream	☐	☐	☐	☐	☐	☐
7. Reduce the urine loss when I cough, laugh, exercise or sneeze	☐	☐	☐	☐	☐	☐
8. Reduce my urine leakage	☐	☐	☐	☐	☐	☐
9. Reduce the sudden need to rush to the toilet	☐	☐	☐	☐	☐	☐

SELF ASSESSMENT GOAL ACHIEVEMENT QUESTIONNAIRE (SAGA)

Protocol No: Subject ID:

Visit No: Date (dd-MMM-yyyy)

FOLLOW-UP ASSESSMENT

Below is a list of goals that you said were important to you at your last visit. Since your last visit, please indicate to what extent you feel you have achieved each goal. Please tick only **ONE** box for each question.

	Did not achieve goal	Somewhat achieved goal	Achieved Goal	Exceeded Goal	Greatly Exceeded Goal
10.	☐	☐	☐	☐	☐
11.	☐	☐	☐	☐	☐
12.	☐	☐	☐	☐	☐
13.	☐	☐	☐	☐	☐
14.	☐	☐	☐	☐	☐

When answering the following question, please think about all of your goals	Did not achieve goal	Somewhat achieved goal	Achieved Goal	Exceeded Goal	Greatly Exceeded Goal
15. Overall, to what extent have you achieved your goal	☐	☐	☐	☐	☐

Bladder Diary
IMPORTANT – PLEASE READ INSTRUCTIONS CAREFULLY

It is very important that you fill in the chart overleaf as accurately as possible over a 3 day period prior to attending your test.

It is designed to help us take a closer look at your fluid intake and output, and leakage if any. It also helps us to plan the right treatment for you.

For each day, record ***how much*** (mls. if possible) and ***what time*** you drink and write it down in the ***IN*** column.

When you go the toilet, measure the urine you pass using a jug (mls. if possible) and write it down in the ***OUT*** column.

If you leak urine, put an X, yes or √ in the ***WET*** column. If you experience urgency i.e a sudden desire to pass urine that is difficult to defer please score 0, 1, 2, 3 or 4 according to the urge score that is described on the next page. Then according to how severe your urgency was please enter the appropriate number in the **URGE SCORE** column.

FOR EXAMPLE:

TIME	DAY 1			
	IN	OUT	WET	URGE SCORE
07: 10 am		140 mls		
08: 30 am	250 mls			
10: 40 am		90	yes	
12: 00 noon		150		2
12:45 pm	200 mls			
02: 00 pm		60		0

This means that you passed 140 mls at 07:10 am and had 250 mls of a drink (maybe a cup of tea with breakfast). At 10:40 you leaked urine and passed 90 mls. At 12:00 noon you had 'moderate urgency' with a score of 2 which according to the urgency score means 'you could postpone voiding for a short while without fear of wetting yourself'.

Please write the time you got up and time you went to bed at the top and bottom of the chart for each day. This allows us to see the difference between what is happening during the day and during the night.

Urogynaecology Department, King's College Hospital
Bladder Diary

Time got up: Time got up: Time got up:

Day 1					Day 2					Day 3				
Time	**In**	**Out**	**Wet**	**Urge Score**	**Time**	**In**	**Out**	**Wet**	**Urge Score**	**Time**	**In**	**Out**	**Wet**	**Urge Score**

Time went to bed: Time went to bed: Time went to bed:

Urge score

0	No urgency: I felt no need to empty my bladder but did so for other reasons
1	Mild Urgency: I could postpone voiding for as long as necessary without fear of wetting myself
2	Moderate Urgency: I could postpone voiding for a short while without fear of wetting myself
3	Severe Urgency: I could not postpone voiding but had to rush to the toilet in order not to wet myself
4	Urge Incontinence: I leaked before arriving at the toilet

Health Research Authority
NRES Committee East of England - Cambridge East
Victoria House
Capital Park
Fulbourn
Cambridge
CB21 5XB

Telephone: 01223 597653
Facsimile: 01223 597645

14 June 2012

angela.rantell@nhs.net

Miss Angela Rantell
Professor of Urogynaecology
King's College Hospital
King's College Hospital NHS Foundation Trust
3rd Floor, GJW
Denmark Hill
London SE5 9RS

Dear Miss Rantell

Study title:	**A 12 week, single centre, open label study to evaluate the effect of fesoterodine flexible dosing regimen on the sexual function of women with overactive bladder.**
REC reference:	**12/EE/0029**
Protocol number:	**AMRPhD1**
EudraCT number:	**2010-023851-27**

Thank you for your letter of 12 June 2012, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Ethical review of research sites

NHS sites

The favourable opinion applies to all NHS sites listed in the application, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Non-NHS sites

The Committee has not yet been notified of the outcome of any site-specific assessment (SSA) for the non-NHS research site(s) taking part in this study. The favourable opinion does not therefore apply to any non-NHS site at present. We will write to you again as soon as one Research Ethics Committee has notified the outcome of a SSA. In the meantime no study procedures should be initiated at non-NHS sites.

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of approvals from host organisations

Clinical trial authorisation must be obtained from the Medicines and Healthcare products Regulatory Agency (MHRA).

The sponsor is asked to provide the Committee with a copy of the notice from the MHRA, either confirming clinical trial authorisation or giving grounds for non-acceptance, as soon as this is available.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Covering Letter from Angie Rantell		22 December 2011
Covering Letter from Angie Rantell enclosing revised IRAS and scientific critique emails		
GP/Consultant Information Sheets	Version 1.0	04 May 2011
Investigator CV - Angela Marie Rantell		09 November 2011
Other: Summary of Product Characteristics - Toviaz		04 April 2011
Other: CV of Linda Cardozo (Academic Supervisor)		10 November 2011
Other: Article used to inform the power calculation		
Other: Data from TESA Study		
Other: MHRA Notice of Acceptance of Amended Request		06 June 2012

Other: The Impact of Fesoterodine on Quality of Life		
Participant Consent Form	Version 1.4	13 October 2011
Participant Information Sheet	Version 1.8	09 March 2012
Protocol	Version 1.9	23 May 2012
Questionnaire: Sexual Quality of life Questionnaire - Female (SQoL-F)		
Questionnaire: Patient Perception of Bladder Control (PPBC)		
Questionnaire: Patient Assessment of Constipation - PAC-QOL		
Questionnaire: Pelvic Organ Prolapse / Urinary Incontinence Sexual Function Questionnaire PISQ-12		
Questionnaire: The King's Health Questionniare		
Questionnaire: Self Assessment Goal Achievement Questionnaire - SAGA		
REC application	Submission Code 48710/279901/1/636	04 January 2012
Referees or other scientific critique report - email from Philip Toozs-Hobson		01 June 2010
Referees or other scientific critique report - email from Noreen Hasmi		05 February 2010
Response to Request for Further Information from Angie Rantell		07 February 2012
Response to Request for Further Information from Angie Rantell		09 March 2012
Response to Request for Further Information from Linda Cardozo		02 April 2012
Response to Request for Further Information from Angie Rantell, Urogynaecology Nurse Specialist		12 June 2012

Statement of compliance

This Committee is recognised by the United Kingdom Ethics Committee Authority under the Medicines for Human Use (Clinical Trials) Regulations 2004, and is authorised to carry out the ethical review of clinical trials of investigational medicinal products.

The Committee is fully compliant with the Regulations as they relate to ethics committees and the conditions and principles of good clinical practice.

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document *"After ethical review – guidance for researchers"* gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

Feedback

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

Further information is available at National Research Ethics Service website > After Review

12/EE/0029	**Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project

Yours sincerely

pp S. Davies

Dr Daryl Rees
Chair

Email: susan.davies@eoe.nhs.uk

Enclosures: "After ethical review – guidance for researchers" [SL-AR1]

Copy to: Jackie Pullen jackie.pullen@kcl.ac.uk
Dr Zoe Harris z.harris@nhs.net

Safeguarding public health

Ms J L Pullen
KING'S COLLEGE LONDON
JOINT CLINICAL TRIALS OFFICE, 16th FLOOR, TOWER WING
GUY'S HOSPITAL, GREAT MAZE POND
LONDON
SE1 9RT
UNITED KINGDOM

06/06/2012

Dear Ms J L Pullen

THE MEDICINES FOR HUMAN USE (CLINICAL TRIALS) REGULATIONS 2004 S.I. 2004/1031

Our Reference:	14523/0237/001-0001
Eudract Number:	2010-023851-27
Product:	Toviaz
Protocol number:	AMRPhD1

NOTICE OF ACCEPTANCE OF AMENDED REQUEST

I am writing to inform you that the Licensing Authority accepts your amended request for a clinical trial authorisation (CTA), received on 30/05/2012.

The authorisation is effective from the date of this letter although your trial may be suspended or terminated at any time by the Licensing Authority in accordance with regulation 31. You must notify the Licensing Authority within 90 days of the trial ending.

Finally, you are reminded that a favourable opinion from the Ethics Committee is also required before this trial can proceed; changes made as part of your amended request may need to be notified to the Ethics Committee.

Yours sincerely,

Clinical Trials Unit
MHRA

Medicines and Healthcare products Regulatory Agency
151 Buckingham Palace Road London SW1W 9SZ
T 0203 080 6000 www.mhra.gov.uk

King's College Hospital NHS
NHS Foundation Trust

Dear Miss Rantell,

Study Title: Fesoterodine and sexual function

Condition of approval: This study has been approved however the portfolio adoption is still outstanding. Any participants recruited before portfolio adoption will not be eligible for CLRN support costs or generate any income for the Woman's Health Division.

In accordance with the Department of Health's Research Governance Framework for Health and Social Care, all research projects taking place within the Trust must receive a favourable opinion from an ethics committee and approval from the Department of Research and Development (R&D) prior to commencement.

- **Ethics number: 12/EE/0029**
- **CSP number: 48710**
- **EudraCT Ref: 2010-023851-27**
- **Sponsor: King's College Hospital**
- **Funder: Pfizer Ltd**
- **End date (as per ethics application): 1/12/2014**
- **Protocol: v1.9**
- **Site: King's College NHS Foundation Trust**
- **R&D approval Date: 16 July 2012**

R&D have reviewed the documentation submitted for this project and I am pleased to inform you that subject to the condition detailed above, we are approving the work to proceed within **King's College Hospital NHS Foundation Trust**. The study has been allocated the Trust R&D registration number **KCH12- 074.** Please quote this registration number in any communications with the R&D Department regarding your project.

Conditions of NHS Permission for research:

- The Principal Investigator must notify R&D of the actual end date of the project.
- The Principal Investigator is responsible for ensuring that Data Protection procedures are observed throughout the course of the project.

- The project must follow the agreed protocol and be conducted in accordance with all Trust Policies and Procedures especially those relating to research and data management.
- R&D must be notified of any changes to the protocol prior to implementation.
- Please submit a copy of the progress report on the anniversary of the Ethics favourable opinion **(14/6/12)**

If appropriate it is recommended that you register with the Current Controlled Trials website; http://isrctn.org/

Please ensure that you are aware of your responsibilities in relation to The Data Protection Act 1998, NHS Confidentiality Code of Practice, NHS Caldicott Report and Caldicott Guardians, the Human Tissue Act 2004, Good Clinical Practice, the NHS Research Governance Framework for Health and Social Care, Second Edition April 2005 and any further legislation released during the time of this study.
Members of the research team must have appropriate substantive or honorary contracts with the Trust prior to the study commencing. Any additional researchers who join the study at a later stage must also hold a suitable contract.

If the project is a clinical trial under the European Union Clinical Trials Directive the following must also be complied with:

1 The EU Directive on Clinical Trials (Directive 2001/20/EC) and UK's implementation of the Directive: The Medicines for Human Use (Clinical Trials) Regulations 2004;
2 The EU Directive on Principles and Guidelines for Good Clinical Practice (EU Commission Directive 2005/28/EC); and UK's implementation of the Directive: The Medicines for Human Use (Clinical Trials) Amendment Regulations 2006;

Amendments
Please ensure that you submit a copy of any amendments made to this study to the R&D Department.

Annual Report
It is obligatory that an annual report is submitted by the Chief Investigator to the research ethics committee, and we ask that a copy is sent to the R&D Department. The yearly period commences from the date of receiving a favourable opinion from the ethics committee.

Should you require any further information please do not hesitate to contact us.

Many thanks for registering your research project

Yours sincerely,

Kirsty Hedditch
Research Governance Coordinator

Appendix A:
PISQ-IR: Sexual Function for Women with: POP, Urinary Incontinence and/or Fecal Incontinence

For More Information or Questions
Email: survey@iuga.org

Q1 Which of the following best describes you:

Not sexually active at all	1 G	Go to item Q2 (Section 1)
Sexually active with or without a partner	2 G	Skip to item Q7 (Section 2)

Section 1: For those who are not Sexually Active

L If you engage in sexual activity please check this box G and skip to Page 3

Q2 The following are a list of reasons why you might not be sexually active, for each one please indicate how strongly you agree or disagree with it as a reason that you are not sexually active.

	STRONGLY AGREE	SOMEWHAT AGREE	SOMEWHAT DISAGREE	STRONGLY DISAGREE
a No partner	G1	G2	G3	G4
b No Interest	G1	G2	G3	G4
c Due to bladder or bowel problems (urinary or fecal incontinence) or due to prolapse (a feeling of or a bulge in the vaginal area)	G1	G2	G3	G4
d Because of my other health problems	G1	G2	G3	G4
e Pain	G1	G2	G3	G4

Q3 How much does the fear of leaking urine and/or stool and/or a bulging in the vagina (either the bladder, rectum or uterus falling out) cause you to avoid or restrict your sexual activity?

1 G Not at All
2 G A Little
3 G Some
4 G A Lot

Q4 For each of the following, please circle the number between 1 and 5 that best represents how you feel about your sex life.

		RATING					
a.	Satisfied	1	2	3	4	5	Dissatisfied
b.	Adequate	1	2	3	4	5	Inadequate

Q5 How strongly do you agree or disagree with each of the following statements:

	STRONGLY AGREE	SOMEWHAT AGREE	SOMEWHAT DISAGREE	STRONGLY DISAGREE
a. I feel frustrated by my sex life	G1	G2	G3	G4
b. I feel sexually inferior because of my incontinence and/or prolapse	G1	G2	G3	G4
c. I feel angry because of the impact that incontinence and/or prolapse has on my sex life	G1	G2	G3	G4

Q6 Overall, how bothersome is it to you that you are not sexually active?

1 G Not at All
2 G A Little
3 G Some
4 G A Lot

End of Items for Not Sexually Active

Section 2: For Those Who are Sexually Active

The remaining items in the survey are about a topic that one is not often asked to report on in a survey please answer as honestly and clearly as you possibly can.

Q7 How often do you feel sexually aroused (physically excited or turned on) during sexual activity?

1 G Never
2 G Rarely
3 G Sometimes
4 G Usually
5 G Always

Q8 When you are involved in sexual activity, how often do you feel each of the following:

	NEVER	RARELY	SOMETIMES	USUALLY	ALMOST ALWAYS
a. Fulfilled	G[1]	G[2]	G[3]	G[4]	G[5]
b. Shame	G[1]	G[2]	G[3]	G[4]	G[5]
c. Fear	G[1]	G[2]	G[3]	G[4]	G[5]

Q9 How often do you leak urine and/or stool with <u>any type</u> of sexual activity?

1 G Never
2 G Rarely
3 G Sometimes
4 G Usually
5 G Always

Q10 Compared to orgasms you have had in the past, how intense are your orgasms now?

1 G Much less intense
2 G Less intense
3 G Same intensity
4 G More intense
5 G Much more intense

Q11 How often do you feel pain during sexual intercourse? (If you don't have intercourse check this box G and skip to the next item.)

1 G Never
2 G Rarely
3 G Sometimes
4 G Usually
5 G Always

Q12 Do you have a sexual partner?

1 G Yes ° Go to Q13
2 G No ° Skip to Q15

Q13 How often does your partner have a problem (lack of arousal, desire, erection ,etc.) that limits your sexual activity?

1 G All of the time
2 G Most of the time
3 G Some of the time
4 G Hardly ever/Rarely

Q14 In general, would you say that your partner has a positive or negative impact on each of the following:

	VERY POSITIVE	SOMEWHAT POSITIVE	SOMEWHAT NEGATIVE	VERY NEGATIVE
a. Your sexual desire	G[1]	G[2]	G[3]	G[4]
b. The frequency of your sexual activity	G[1]	G[2]	G[3]	G[4]

Q15 When you are involved in sexual activity, how often do you feel that you want more?

1 G Never
2 G Rarely
3 G Sometimes
4 G Usually
5 G Always

Q16 How frequently do you have sexual desire, this may include wanting to have sex, having sexual thoughts or fantasies, etc.?

1 G Daily
2 G Weekly
3 G Monthly
4 G Less often than once a Month 5
G Never

Q17 How would you rate your level (degree) of sexual desire or interest?

1 G Very high
2 G High
3 G Moderate
4 G Low
5 G Very low or none at all

Q18 How much does the fear of leaking urine, stool and/or a bulging in the vagina(prolapse) cause you to avoid sexual activity?

1 G Not at All
2 G A Little
3 G Some
4 G A Lot

Q19 For each of the following, please circle the number between 1 and 5 that best represents how you feel about your sex life.

		RATING					
a	Satisfied	1	2	3	4	5	Dissatisfied
b	Adequate	1	2	3	4	5	Inadequate
c	Confident	1	2	3	4	5	Not Confident

Q20 How strongly do you agree or disagree with each of the following statements:

	STRONGLY AGREE	SOMEWHAT AGREE	SOMEWHAT DISAGREE	STRONGLY DISAGREE
a. I feel frustrated by my sex life	G[1]	G[2]	G[3]	G[4]
b. I feel sexually inferior because of my incontinence and/or prolapse	G[1]	G[2]	G[3]	G[4]
c. I feel embarrassed about my sex life	G[1]	G[2]	G[3]	G[4]

d. I feel angry because of the impact that incontinence and/or prolapse has on my sex life	G^1	G^2	G^3	G^4

King's College Hospital ***NHS***
NHS Foundation Trust
Denmark Hill
London
SE5 9RS

Dear Patient

My name is Angie Rantell and I am the Lead Nurse in the Urogynaecology Department at King's College Hospital. I am currently undertaking a PhD assessing the impact of bladder symptoms on the sexual function of women attending our unit.

As part of the study I am planning to run two focus groups. A focus group is where we assemble a group of women to discuss a topic and provide feedback. I specifically wish to encourage women in this group to discuss how they feel about discussing sexual function with health care professionals and how you feel it is best for us to approach this subject during a consultation.

If you would be happy to join in one of these focus groups then please let me know either by email or by telephone – details below.

angela.rantell@nhs.net
0203 299 3457 (answerphone is checked daily)

The discussion will last approximately 1 hour and you will be provided with refreshments and receive a Marks and Spencer's gift voucher to compensate you for your time. You will be asked to complete a consent form at the start of the focus group but your identity will remain anonymous for the course of the discussion and in any write up and evaluation of the outcomes. You will be free to leave at any time during the discussion.

If you wish to participate, I look forward to hearing from you or if you would like further information before joining please do contact me by phone or email.
The focus groups will take place on

Thursday 4th May – Arrive at 2pm, discussion to start at 2.30, finish by 3.30

Wednesday 10th May - Arrive at 6pm, discussion to start at 6.30, finish by 7.30

Both will take place at King's College Hospital, Denmark Hill, London, SE5 9RS.

Further information will be provided on agreement to attend.

Thank you in advance for your consideration.

Kind Regards

Angie Rantell
Lead Nurse Urogynaecology

Patient Information Sheet

1. Introduction

You are being invited to take part in a focus group. Before you decide to take part, it is important for you to understand why this research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information.

2. What is the purpose of the study?

The focus group aims to encourage women who have been seen in the Urogynaecology clinic in King's College Hospital to help us to understand how sexual function should be discussed during a consultation in a gynaecology clinic. We wish to understand how you would like clinicians to approach the subject and the barriers that hinder discussion. We are happy to hear from women who are or are not sexually active.

3. Why have I been chosen?

You have been identified as a potential participant in this focus group. We would like to recruit 20 women from our clinics to participate in two groups.

4. Do I have to take part?

It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and given time to review the information.
If you decide not to take part, you do not have to give a reason. If you decide to take part you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive.

5. What will happen to me if I take part?

If you take part in this study, your involvement will last approximately 1 .5 hours. The first 30 minutes will be for administrative tasks when you will be required to sign an informed consent form to agree to participate. Following this you will be asked to participate in a discussion with a group of women for approximately one hour. We hope you share your personal views with us and comment on other women's ideas to help us to understand why you agree or disagree with their views. If you have had particular experiences (good and bad) that have helped to shape your views we would encourage you to share these with us.

6. What do I have to do?

If you wish to take part in this study you will be asked to:

- Attend the focus group at the time agreed
- Participate in the discussion
- Share your own views on the topic

7. What are the possible benefits of taking part?

The information we gain from this study might help us to approach the topic of sexual function in women attending the gynaecology clinics in a more thoughtful, user friendly manner.

8. What are the possible disadvantages and risks of taking part?

There are no physical risks to participation and it will not affect your care within the department. However, you will be asked to share your personal opinions and possible experiences with other women. Although we will not be making reference to any individuals diagnosis or treatment plan during the course of the session, potentially, women may feel embarrassed about the discussions given the sensitive nature of the topic.

9. Payment

You will receive a £50 Marks and Spencer's voucher at the end of the group session to reimburse you for your time.

10. Will my taking part in this study be kept confidential?

If you join the focus group, the nurses and other hospital personnel involved in this study may need access to your medical history for the purposes of this study. By signing the consent form you agree that the study personnel can access your medical history.

No names will be used during the discussions and your identity will be kept anonymous during the focus group.

Some of the data collected may be seen by monitors, auditors, ethics committees and other authorised individuals from King's College Hospital NHS Trust (the sponsor of this research), and representatives of regulatory authorities, to check that the study is being carried out correctly. They will all have a duty of confidentiality to you as a research participant. By signing the consent form you agree to this access for the study.

Any records identifying you will be kept confidential and won't be made publicly available.

11. What will happen to the results of the study?

Once all the focus group results are available the study nurse will be happy to discuss this with you. A final report will be produced and may be published. A copy of the publication will be available from King's College Hospital on request. Please note that your name will not appear in the final report or publication. This study is part of an educational project.

12. Who is funding the study?

This study is being funded by an Investigator Initiated Research Grant from Pfizer Ltd. Some members of the Urogynaecology team perform consultancy work for Pfizer Ltd.

13. Contact names and telephone numbers for further information

For any concerns or other questions about this study, please contact:

Angie Rantell 0203 299 3568

angela.rantell@nhs.net

For any concerns about your rights as a participant or any complaints please contact the Patient Advice and Liaison Service (PALS). This is a service that offers support, information and assistance to patients, relatives and visitors. They can also provide help and advice if you have a concern or complaint that staff have not been able to resolve for you. The PALS office is located on the ground floor of the Hambleden Wing, near the main entrance on Bessemer Road - staff will be happy to direct you.

Tel: 020 3299 3601
Textphone: 020 3299 1878

Fax: 020 3299 3626
Email: kch-tr.PALS@nhs.net

Before you sign the informed consent form, you should ask questions about anything that you do not understand. The study staff will answer any questions before, during and after the study.

Thank you for taking the time to read this information sheet.

King's College Hospital NHS
NHS Foundation Trust

Centre: King's College Hospital
Patient identification Number for this Group: _____

CONSENT FORM

Focus group
Assessing the Sexual function of women attending a gynaecology clinic

Name of Researcher: Professor Linda Cardozo, FRCOG and Angie Rantell BSc (Hons) RN.

Please initial box

1. I confirm that I have read and understand the information sheet (version 1.0 dated 12/04/2017) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected ☐

3. I understand that relevant sections of any of my medical notes and data collected during the study may be looked at by responsible representatives of the sponsor or the NHS trust, the ethics committee and regulatory authorities, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records ☐

4. I agree to take part in the above study ☐

Name of Patient	Date	Signature
Name of person taking consent	Date	Signature

When completed: Original for researcher site file; a copy for the participant; a copy for the medical notes.

Angela Rantell
Lead Nurse, Urogynaecology
PhD Researcher

Introductions

Cathy Davis – Nurse Specialist – scribe

Patient 1;2;3;4;5;6;7

Reason behind the group: as part of my work I was trying to investigate how treatment affects sexual function in women with an overactive bladder. When women come to see us in the Urogynaecology clinic, what are the issues about discussing sexual function; what do we do well; what do we do badly; how do you want us to approach it. I want you to tell me your experiences; how you think something should be done; what you would like from us and I will have a few questions to prompt along the way.

Confidentiality: Everything will stay in this room; please feel free to share – you don't have to share your personal experiences if you do not wish, but I would like your opinion, ideas and thoughts.

Question 1:

When you have been to your GP, you get referred to the Urogynaecology Clinic and we are going to see you and start taking a history; how do you think we should approach the subject of sexual activity and sexual function?

Patient 1: I think it depends on the person who is coming along; there could be a religious issue and that has to be taken into consideration. Some people are more broad minded than others and are able to discuss things quite openly and then equally, you will have some patients who are quite closed up and would feel quite uncomfortable, so there are quite a few things to take on board. I think having a written question and answer, rather than a verbal conversation, would make it a lot easier, so that you can tick boxes and that might be a way of lessening the embarrassment for some patients.

So, depending what you tick on the form means we would bring up the subject or not?

Patient 1: Yes, or you could even have a question on the form e.g. if there was some sexual activity, then you could fill in a box, possibly.

Patient 5: I think the doctors should be allowed to express their concern with sexual activity before the patient comes, because a lot of people have got more trust in the doctors than when they are coming here for the first time. They won't seem so uncomfortable when they come here. From experience, I feel that.

Patient 2: I think questionnaires are a good way of maybe gaining consent, in the broad sense of the word. The problem is that it is all down to the questions; I did feel that some of the questions now would not apply to me. If I remember rightly, they are structured such that I did not really know what to put down on the form and sometimes that tick box, with something that is personal like sex, doesn't always apply in the same way as; how many times do you pee a day; how many times do you have to get up in the night. So that would be my caution against; I am going on personal experience and the questionnaire did not help me at all, but I am open-minded.

Patient ?: I don't mind generally chatting, especially if the clinician is female it's a lot easier. I have had to have an examination by the two Gynae guys and they have always been either older men or female and they were a lot younger than me and that was excruciatingly embarrassing…it was just awful. I know they have to do it, but I felt very embarrassed.

Patient ?: Age is an interesting thing, but maybe we will come on to that.

Patient 7: I also think a lot of patients come with somebody; a friend, husband. Even with your husband sitting there, who you are obviously intimate with, I think a lot of people would not be comfortable talking about their issues with sex with their husband, with their husband sitting there, and more so if it is just a friend. I think you need to be mindful of the fact that, if you have a patient in front of you who has someone with them, you are less likely to get as much information and them be as open as you would need them to be with their companion in the room.

Patient 6: I have been coming for a lot of years and had a lot of things done, but I agree with you; I have had men to do the one where you do the weeing and all that sort of thing and it is totally embarrassing when you have to wee and then come back. You want to die really…you feel happier with a woman, but I think that because of what we do, it's not really something that you want a man to see. I'm sure they don't think anything of it and I've always found them to be really lovely, but you think why a man would want to do this. I have been coming a lot of years, but I have never been put in a place where I have felt uncomfortable; it has always been on a form. Nobody has really asked me where I felt embarrassed. I've never been put in that position. It is something you want to gloss over; for me, having an overactive bladder has made me ashamed to tell people I've got it. Even girlfriends; I go away with my girlfriends once a year and because I wear a pad; if share with someone and I hide it and not let them see that I wear them because they make jokes about the Tena lady on the TV and I feel embarrassed, so I hide it. It's one of those things that you don't really want to talk about. I don't know if you agree?

Patient 2: I definitely concur. You have got the shame of having an overactive bladder and then talking about very personal issues. I agree with Patient 7; I am not in a partnership any more and I would not have wanted to discuss our sex life with him alongside me. It does not matter for me so much if it is a man or a woman, but I think that, not to big up Kings, this is a much better department than in some other places. There were things within the dynamics of me and that partnership and I am very open-minded, the last thing I would have wanted to discuss would have been our sex life with him sitting there.

Patient 6: I would say that as well. I don't know if you all agree; it's not one of those things that you don't really want to talk about. It's almost like you are ashamed. Even my husband asked me today where I was going. I said I was just going up the hospital and he asked if it was getting any better and I said yes, but he doesn't really want to know. It's something they don't want to delve into.

Patient 5: I have a different experience because I went through a very, very early menopause, so my husband grew up with me going through all that, so I'm not embarrassed of talking to a man, not all men; my son understands; my husband; close family and the doctors.

But with the bladder problem though, do you still talk about it?

Patient 5: I still talk about it to my family and anyone. I really do find you do benefit from it; they understand, so when I'm going out anywhere, they say that they will have to make sure we are near loos for me; I don't put my life on hold.

Patient ?: I find my friends easier to talk to; we are the same age and got the same issues, especially if you've had a couple of kids; we have a joke and laugh about it, but it's not something I would discuss with people at work.

Patient 2: I've noticed; I don't have children and am in my late 40s, but with friends that have, there is a bit of this; I went to the gym and had a little bit of an accident; so it has opened up; but for years, having had an overactive bladder all my life and the shame throughout my whole life and the impact that that has had on my sexuality; it is very difficult to just turn that around in 5 minutes. When I had to do the whole urodynamics testing and I have had it done twice here now and the second time, the young gynaecologist came and asked if he could do an internal examination and I don't have an issue with that so much; whether it is a man or a woman.

Patient 3: I do agree, but I don't discuss sex life with my son, he is a doctor. I came here with a prolapse problem. At that moment I was going through a hard time, so I thought that it was best to open out with him. I told him my problem and he was very open with me and he helped me.

Did it feel better talking to him?

I felt better; I felt, well he is a doctor; let me ask him about it, because the operation is going to take a long time.

Question 2:

Thinking about when people come to clinic that have bladder or prolapse problems, that aren't sexually active; what are people's views on how far health care professionals should delve into why they are not sexually active?

It depends whether it was relevant or not. I think a lot of the time it wouldn't be, would it?

Ultimately, it is trying to understand the difference between not sexually active because of lack of a partner or through choice; or because of a problem that we could potentially help with.

Patient 5: Mine is through choice after my husband passed away 25 years ago.

If someone asked you that, you would be happy to share that with them?

Patient 5: Yes.

Patient 4: I have not been sexually active over the past years and I find it embarrassing to talk about it; especially when some of my friends ask how come I am not doing it and then I get all embarrassed about it and people are always question about it and I get embarrassed and sometimes I even lie about it and say I am having it and I'm not. One of my friends said that she sees I have two children, but she has never seen me with a man; what is wrong with you. I am very embarrassed and I say that my partner is living abroad; I find different excuses. Then I go to the doctor and he will ask me why I am not sexually active and sometimes I do not know the answer to give him because I don't know.

Patient 2: Talking from personal experience; I think it is important not to exclude people, or having a conversation with people, because just because they are not sexually active, that is only at the time you are asking them and also, there are all sorts of reasons; we were talking about the shame over so many years, both psychological and physical and also that there might not be a decent guy

around, that if I had not been asked that question, I would have been quite upset because it is almost negating part of me as a woman and I think we all have the ability to be sexually active and if it becomes an exercise in exclusion, that would make me feel really sad.

Patient 6: Do you think that they are linked then? Do you think the overactive bladder is linked?

There is evidence to say that women with an overactive bladder have less sexual activity and some avoid sexual activity; more with prolapse; but that's ultimately what we are trying to understand when we are asking the questions. Is it because of the bladder, bowel or prolapse problem, or is it because of external reasons that we don't need to go into.

Patient 7: You have basically touched on what I was going to say which was, how you ask the question. You can ask the question, "Are you sexually active" and if they say yes/no, you can tactfully ask "Is that through choice"; "would you like to be more sexually active, but you find that this problem prevents you, or is it because of other factors which are not relevant to why you are here" and depending on how they answer then that would depend on how you perceive.

Patient 4: Since I had my hysterectomy done, I have not got a partner, but am not really interested because I do not feel that I want to have sex and that's over about 10 years and I have not had intercourse since then. Now the bladder problem, the prolapse problem, everything put me off. I have no feeling down below.

Patient 6: I think also that now people talk about bladder problems, but when I first had it, there were no adverts on telly for pads and it really was taboo. I can remember when you would go and buy sanitary towels and they would put them in a brown bag so nobody would see them. Now it is much more talked about, but I still don't feel that it is something I want to go and shout about. I still feel that it is something personal to you.

Question 3:

If, when you came into clinic we didn't ask about it; what would make you volunteer something about it or ask questions yourself?

Patient 7: If you felt it was an issue for you and you weren't embarrassed to do so; but I think a lot of people, it might be an issue for them and if you don't ask them, they are not going to speak up.

Patient 6: I think that if you feel it is linked to the problem, I think you should ask; only if you think it was relevant. You are not asking just to be nosey, but if it is linked to the problem, then you should ask.

Patient ?: I think Patient 7 touched on it and it's having a question or even a consent to ask would you be happy to discuss your sex life, or it would be in similar terms and then you are giving some agency to us women to then go forward with that and I think the other important thing is menopause, which I haven't hit yet, I am Perimenopausal and I think that it is very important that historically, women of a certain age, once child rearing years have gone, it's almost as if you don't matter; it's like you retreat back into being a shadow. That's why I think discussing a patient's sex life, whether or not they are having it, not having it, want it, why, is very important; otherwise it is a bit like we are being put out to grass.

Patient 7: I think another thing you have to differentiate between is what has started off as not having sex because of your issues, which then goes in to not having any sex drive because you have

been without it for so long, you have lost that sex drive. So there is nothing to say that a woman, if she met a man that she was interested in, that he might actually resurrect that sex drive in her, but a lot of women will just dismiss it because they don't have a sex drive anymore; but what started that? Was it abstaining because of the problem and then you have now gone without for so long; naturally that is what happens to human beings, men and women, the sex drive disappears and that is a bit more difficult to get around, because I think a lot of women might just go without because they are no longer feeling that sex drive because they have gone without it so long; but they could actually resume a very healthy sex life with the right person and with their problem being sorted out.

Anybody else have any comments on that?

Patient ?: It has always been on the form, going back and back, it's always a question isn't it, but you don't think it is very important, maybe.

Patient 4: Since my operation I have noticed it.

Question 4:

One of the other things, when it comes to asking women about sexual activity, we know that certain type of sexual activity are actually linked to certain types of problems; so we know, for women who come with recurrent urine infections, potentially it can be because of sexual practice, anal sex and things like that. What are people's views on, if they say they have bladder and bowel symptoms and they are sexually active; how do you feel when someone asks you if you are having vaginal sex, anal sex, masturbation and that sort of thing?

Patient 1: I was asked that a number of years ago, it wasn't for urogynae, but it was for piles. That was quite embarrassing, because I wasn't expecting the question. As I was being examined, the consultant asked if I have anal sex (intercourse) and I was so taken aback that I asked him if he did. It took me off guard and I didn't expect it; it was very embarrassing.

Patient 2: I can't remember where I saw it, but a couple of weeks' ago I read an interesting article, that given that sexual practices are changing, whatever that means, that there does need to be more questions asked about those individual practices. Otherwise you are not getting a full picture. If someone is engaging in a particular practice and that is causing an issue…

The latest National Survey showed that, yes, sexual practices are changing. For women over the past 30 years, more women are having same sex relationships; more women are having anal sex; more women are masturbating in comparison to numbers years ago and less women are having vaginal intercourse.

Patient 7: Is that vaginal intercourse per se or less women are having it as the general form of sex?

As the general form of sex.

Patient 6: Do you think that that is linked to problems?

We don't know.

Patient 7: My daughter is 19 and my son is 18 and their sex lives are completely different to mine at that age. My daughter is as happy with a girl as a guy and is very experimental. With both of them,

nothing is off limits; nothing is taboo. Their friends are all the same and they are very open and are not embarrassed to talk about it; I'm very fortunate like that.

Patient 6: When I was young, nobody talked about anything like that. When you had your period, it was your curse; you did not talk to your mum about anything like that. My mum told me about sex life when I was 11. With my children now, if I say anything about it they tell me to shut up because they can't bear it!

Patient ?: So women are having less vaginal sex. Well can't you mix and match; have oral and vaginal.

Many women are mixing and matching. As their primary type of sexual activity, less women are having vaginal sex.

Patient ?: Maybe it's because it's less of a case of years ago with the lights out and the nighty went over the head.

Patient ?: Attitudes have changed though haven't they. Even sex education for my children at 14 and 18; when my son came back and told me about sex education, I nearly fell over; it was very graphic; but my son, even at age 14, was quite happy to tell me what was discussed and it brought up lots of things; specific acts, which I was quite shocked at, because I didn't talk to my mother about it. People are more open now.

Patient 6: My son is a school teacher of seniors and he has a transgender in his class. That is a whole new thing of how to handle that. He is a PE teacher and this is a girl who wants to be a boy. When he tells me how he has to hide it from the other kids and has to still address him as a boy because he hasn't changed yet. His partner is a primary school teacher who teaches little ones and even then, with the 4 and 5 year olds, she can still tell sometimes by how they play, that they are not coming from very good homes, because of how they play with one another. This is something you would not have thought of with a 5 year old where they are coming from homes where things aren't right. You have all these things that we wouldn't even have dreamt about.

Patient ?: I suppose the overactive bladder is seen, well I've got this idea, that it is for older ladies, but actually, if I have had it all my life, then many other women have had it all their life. So, when you are doing a sexual practices questionnaire, obviously you would have to be very cautious because, probably, if you were to give "do you do this, this, this and this" some peoples eyeballs might fall out. So that is a really difficult one.

Patient 6: But that probably would really help you though wouldn't it, if people were really honest? Alright, my days are gone, but for people who are in that age group, I suppose that would be really helpful, but I don't know if people would want to do it.

Patient 7: I think, given the option, if they are happy to complete a very personal questionnaire; explain it would be very useful and it might help in their treatment. Give them the option; there is a questionnaire we would like you to complete; however, it is extremely personal, some might say invasive, if you are comfortable with it, fine, but if not you don't have to complete it.

Patient 2: But then, if say you are using the example, I presume you are talking about UTIs and anal sex. They might not be having UTIs at all, it might not be relevant, so then is it better to have a casual conversation with the female patient, because then you are a bit more led…I sometimes wonder, it's a bit like "how much do you drink", "do you do this" no I don't.

Question 5:

So that's a really interesting question for you all…do you think people always tell the truth? Do you think people are always truthful when we ask them?

Group: No

What do you think people aren't truthful about?

Patient 7: They don't want to be judged primarily. People make a judgment on you within the first few minutes; although clinicians don't do that, but you do feel that, you do feel like you are being judged.

Patient 6: Even if you did do all those things that you were saying, would you want to tell people, because would you not be ashamed? Would you think "I'm not telling them that"…even if you did do it; you would really want to…they would think this and that. With drink; when it's on the form, you think "what should I put?"…do you put what I think they want me to put.

Patient 7: My ex-husband was actually an alcoholic unfortunately. I had been telling him for years he had a problem, sometimes he listened; sometimes he didn't. After we divorced, he asked me to go with him as he had to have a medical and one of the questions the GP asked him was how much he drank. He came out and he was really shaken and he said "I really have got a problem haven't I?" I asked what the doctor had said and he said "he asked what I drank and I lied; I halved it and he still turned around and called me an alcoholic". He completely lied even though it was very serious and important that he was honest.

There is evidence to say that, when men are asked to say about sexual function the most commons things they lie about are erection quality, size and how often.

Question 6:

So what do you think the particular aspects of sexual function that women are probably least likely to be honest about?

Group: Number of partners; how many times they do it. Number of partners is probably the biggest one.

Patient ?: If they are having relationships with more than one person – a lady might be in a relationship, but may actually have someone on the side and be less likely to admit to that.

Patient ?: That's really important, because you tend to think in terms of questionnaires that its…you might be single like me, or you might have a partner; but if people are having affairs; they might, they might not, but it does have a bearing.

Patient ?: Again, if you are asking these questions with the husband there and she's having an affair and she is asked how many times a week she is having sex!

Patient ?: I think men are a lot more het up about prowess than women; although, I think that may be changing now, because with the increase in pornography; not my cup of tea; but I speak to younger women and it seems that sex is becoming a bit of a performance art now, rather than just being intimate and enjoying something with somebody, it's meant to be "how well am I doing

this/that", so it's almost taking on that male thing. But what you have just said about multiple partners…it is relevant.

Question 7:

So coming back to that clinic appointment when we are asking questions…when do you think it is appropriate to ask you about sexual function and activity? At what point in the conversation? At what point in your journey? Is it something we should be going into on the first appointment? Is it one of the first questions we should ask?

Patient 7: Because it is such a highly personal thing and a lot of people would be very uncomfortable being asked it straight off. I think you have got to establish, for want of a better way of putting it, a relationship with your patient before you can broach something like that.

Patient 6: I think also that if it's a woman or a man asking you makes a difference. I think you would be much happier telling a woman than a man.

Patient 3: Yes, you feel more comfortable with a woman. When I came the first time, she asked me when did you last have sex and her colleague was sitting there as well and I didn't know what to say, I just said, last week, even though I hadn't. I just had to say, thinking she might think I wasn't having any personal relationship, but because of the prolapse, I just didn't feel comfortable at that time and that was the only reason.

Patient ?: JB is lovely, but I could not sit here and talk to him in the same way.

Patient 7: If you are going to introduce that conversation with a patient, it would be better to have a female nurse or doctor, someone trained to specifically cover that are, rather than…I know that the consultants are specialists, but if they are male, you are not going to get the answers that you need as much as if you had somebody, a nurse who was specially trained to sensitively deal with that aspect.

Patient 6: I think it depends who asks you the question and how comfortable you feel with them. Someone like yourself, you would feel quite comfortable saying that.

Patient ?: ***sorry ange…can't hear this so good!***

Patient 6: If you have said that it would be helpful to us…if you said, "I'm not asking this to be nosey, but it would really help us in our research if I ask you this question" so that people know that you are not asking it as a matter of course.

Patient ?: I don't think it is just for research, it's for the benefit of the patient too.

Patient 2: I also, it's relevant to the question but perhaps going off on a little bit of a tangent, but budgets are being cut and I was reading about somewhere in Germany where they were using, and I don't like the term peer support, but they were not exactly focus groups, so that the information was captured where there wasn't the time or the resources to have a woman or a nurse on, rather than clamming up in front of a male doctor or consultant.

Patient 7: Maybe also, for those who still feel uncomfortable talking to another being, whether they are female or whatever, you could offer the option of the questionnaire.

Question 7:

So, as well as the questionnaire, what other things can we as clinicians do to make you more comfortable to discuss that with us? What are you looking for to feel that comfort to be able to discuss?

Patient 6: I don't think you could do any more really. I think, just make sure it is a woman and not a man and I think you would just be embarrassed saying that to a man…well most people, not everybody, but I think if it was a woman asking it, I don't think you could do any more.

Patient 7: I think maybe if you make them feel that they are not alone; if you were to say "we find that a lot of our patients experience this", they might say, "oh yes, I had that", but also it would cover the bit where you are making them realise that it's not unique to them; they are not alone in that problem and I think that would make them feel more comfortable discussing it.

Patient 6: I just think that women make a joke of it. I work with a girl who says about the advert for Tena lady…why is she smiling…I wouldn't be smiling if I was weeing myself jumping up and down…and because people make jokes like that: she's one of the girls I go away with I wouldn't dare say that I wear them.

Group: She is probably wearing them. She's wearing Always, couldn't afford the Tena's. It's a jealousy thing.

Patient 6: That's why I hide mine, because I don't want anyone to see them. I feel ashamed and I feel that if they know I wear them, they probably wouldn't, but I don't want to be the butt of their jokes, I don't want them to see that I wear them, which is silly really.

Patient ?: Can I ask why more women are not offered things like TVT's, because I think so many women assume that they have to live with this problem and their only way of getting through life is with pull-up pants and Tena lady?

Going off on a tangent; it's actually because it is not suitable for all women. People with overactive bladder and things like that, doing a TVT will make them worse and so it is not a suitable form of surgery for everybody with incontinence, because there are lots of different types of incontinence.

Question 8:

Apart from being a woman, what other factors may prevent you from opening up? Ignore the fact that it's a man, if it is a woman asking the questions, what other things may prevent you from opening up to the woman and answering questions about sexual function?

Patient ?: I think it just depends on the individual. Some people just will never be comfortable discussing with someone they don't know, or even with their partners. It's the individual personality.

Patient 7: I also think it is depending who is asking the questions; they have got to make you feel at ease. If you've got someone who is really officious, treating it like a school exercise, you are not going to feel as comfortable as someone who is kinder, has the gentle approach.

Patient ?: As with any relationship, emotional, professional, whatever; it does come down to dynamics and maybe there are just some people who will never want to open up and you just have to factor that in and then there are others, who are probably not best professionals who aren't best placed to be asking those questions because they don't have the empathy or the understanding. We are talking about men and women, but I have come across male doctors in the past who have had far more empathy than women doctors.

Patient 6: I just think that if a man asks you that though, you just straight away have that sort of embarrassment with a man, whereas, if a woman asks you, I think you feel that bit more comfortable. I know that they would not just be asking you for the sake of it, but for me being an older lady, I just feel that I don't know if I could answer.

Patient ?: Well it's a bit like personal grooming, the number of women that say "I've got a Gynae appointment tomorrow and I haven't had a wax", but you think to yourself, I'm sure they are really not bothered.

Patient ?: I know it sounds silly, but I would feel more comfortable discussing it with a 65 year old guy than some Greek God, tanned, sitting opposite me; I could not meet their eye and discuss anything.

Patient ?: That's an interesting thing…age. I think that with age does come a bit more empathy and understanding; not necessarily, but I think that I would feel much better happier discussing things of a sexual nature, male or female, with someone who is not a young pup, for want of a better word. Just because life brings about experiences, so for me age is just as important as gender.

Question 9:

Anything about the environment you are doing it in. A lot of you have gone through Urodynamic tests or come along to different clinic appointments, Nurse-led or Physiotherapy and they are all in slightly different environments that have made you feel more comfortable? What environment would make you the most comfortable to chat openly and honestly?

Patient 3: If it was a mature person, then you would be more comfortable, but young doctors have to learn as well. They need to be there as well, but you do feel, oh it's a young person.

Patient 6: Is that the one where they x-ray you…that is sole destroying that one.

Patient ?: I was so glad I did it though, because when I was first diagnosed 10 years ago, it was just a relief. Your office is quite nice…that's the nicest office. You and the other lady that I see are both so lovely. I like the way Urodynamics is tucked out the way.

Question 10:

We mentioned earlier about when friends or relatives or partners come to the appointment with you. If we wanted to ask questions and your partners were there, what are you views on whether we ask your partner to leave the room and then ask you questions; how do you want us to broach the subject, because ultimately there are times when we have to ask you certain questions, but yes we understand that if there are people with you, you may not want them to know the answers, so how do you want us to approach that situation?

Patient 7: I think you need to ask the patient before they attend the appointment, because I know that if I came with my husband and you said that you wanted to ask some sensitive questions about my sex life and would I like him to stay or go; I would feel really uncomfortable asking him to leave the room, I know I would worry about how he felt about that. I think if possible, I would prefer to be asked before I arrived at the appointment; then at the appointment you could ask him to step outside for a while and it wouldn't look like you have had them banished from the room.

Group: I wouldn't bring my friend along. Nor me. Some people would. Ultimately, you may want to lie or not be truthful.

I think often women and men, when they are coming for an appointment they worry that they are not going to remember everything, so they have someone else there to help them go through everything to make sure they have understood everything and remember everything, but it is how close is that person and what do you want them to know.

Patient ?: I think it is up to the individual. I feel more comfortable coming alone. Even when I did have problems going back a few years ago, my husband said that he didn't feel comfortable coming, so I go home and tell him what was going on.

Group: My husband wouldn't be interested at all. I'm sure there are plenty of people who come with somebody.

Patient ?: I think your point about there being a sort of proviso in the appointment letter; I haven't mentioned before that sometimes the way the appointment letters are structured I can't work out what's going on, but so people are aware that there might be a part of the consultation where it might be an idea just for the medical professional and patient to be on our own.

Question 11:

There is a group of people who come along to appointments and they haven't completed any paperwork and they haven't done the questionnaires and there is a group of people who either can't read or write or don't have the appropriate language skills to have been able to answer in advance. How do you think we can get around that?

Patient 7: You can only phone. I think you need to speak to the patient. You can't assume that they have read the letter, or that they have received it. Sometimes you get told on the phone about the appointment, but you don't always receive the back-up letter, so I think the safest way is to speak to the patient.

Patient ?: Language is an interesting one. It could be someone who speaks a different linguistic language or maybe who has communication difficulties and their opinions are just as relevant and important as ours.

Patient 7: There is also the ethnic issue where some women have to have a chaperone, in which case only a woman could approach those questions. But I don't know what you do then about asking the guy to leave the room. I think that from a medical point of view that's okay, providing it's a female, if they can't be left alone with males.

Patient 6: None of us are perfect, but I think if people haven't filled in the forms and not done their diaries, there is only so much that medical professionals can do for people. If people continually

don't adhere, not that you necessarily want to wash your hands of them, but there is only a certain amount that you can do.

Patient ?: People have got to help themselves. It is like a smoker, people have got to help themselves and obviously, everyone here wants to get better.

Patient 6: And this is a valuable resource; if people are a bit half-hearted about it; nobody likes living with an overactive bladder, but people like Ange can't do everything for everybody.

Question 12:

This is for each of you individually to give me an answer on this one. If you were coming into the clinic again, what would be the biggest faux pas or mistake that someone could make when initiating the subject of sexual activity with you?

Patient ?: You have to ask the question haven't you, but maybe we don't mind sitting around the table and talking about it, but the individual most probably wants to be taken aside very quietly and asked the question. I remember when I was working with the elderly I used to have to bring them, but even though they knew me, they wanted to talk about that privately.

Patient 2: It's not a faux pas as such, but "are you sexually active". What does sexually active mean? We talked about people being in long term relationships and not having sex from one year to the next. I felt that is a difficult question because, I felt that when someone asks me that, it is something I get a bit fed up about, I would like to be in a relationship. I think it is wording things so that they are as inclusive as possible so as not to deny someone the opportunity, so maybe not say "are you sexually active" yes or no, it's not being too directional.

Question 13:

So maybe a better question for you would be; when you are in a consultation and someone is going to ask you about sexual activity or sexual function, what is the question you would like them to ask you?

Patient 6: I think the thing would be to say "are you sexually active at the moment".

So, just coming out with "are you sexually active at the moment", you would be happy with?

Patient 6: Yes, "are you sexually active at the moment, only it is an issue that we need to know about, not to be personal, but it does help with our thing"

Patient ?: Or "are you sexually active and maybe if you're not would you like to be sexually active", just so you are opening it out a bit. So when I first saw Angie a year ago, so I came 10 years ago and when I filled in the form I was sexually active then; two weeks later the four year relationship came to an end, thankfully, so by the time I saw her, I was not sexually active. Had I filled in that form a little bit later, I would not have been sexually active; I wouldn't probably even have met Angie and I wouldn't have had the discussions that I have had now.

Patient 6: But if you go into a new relationship now, would having an overactive bladder affect you.

Patient ?: Yes. But what I'm saying is that "are you sexually active now"…could be a bit…

Patient ?: If you say no you could just gloss over it altogether.

Patient 6: But if you met a new partner now would you tell him that you have got an overactive bladder or would you just not mention it.

Patient ?: That would depend on the guy.

Patient 6: This is what I'm saying; my husband would never really talk about it. When I had my hysterectomy I got up that morning and my friend took me to hospital and he called up the stairs "let me know when you want me to come and see you" and went out the front door, because he just didn't and couldn't talk about it…you know, just let me know when you want me to come in and see you.

Patient ?: I just think that there are a lot of women, there are quite a few women, we are not just talking about sexual activity, we are talking about sexual satisfaction.

Patient 6: It's not something you would tell someone on your first date.

Patient ? No. But that's an interesting point is sexual satisfaction, because…

Patient ? I think it depends on the relevance of asking the question of are you sexually active. If you are asking the question in relation to their problem, then I think you would have to expand on that.

Patient ? That's my point, if you think it's to do with your problem then I think you would feel happier.

The general rule of when people are trained to do histories is that they say "are you sexually active, yes or no" and if you say no, a lot of people don't ask any more questions, if you say yes, they say ask if you have any problems.

Patient ? I think maybe, "A lot of our patients with similar problems to yours experience difficulties in their sex lives; do you have any issues; are you sexually active; if not, is that because of your issues". It's not so brutal. "A lot of our patients experience problems, would that apply to you?"

Patient ? Then you are not closing the discussion down because yes and no, that's it, the conversation has gone dead.

Patient ? Nothing's black and white is it. There are shades of grey in between, many shades of grey.

Group: Fifty shades of grey!

Patient 4: That is true, when they ask that question and you say no, some doctors leave it alone; they don't ask a further question.

Patient ? That can be completely misleading to your case and then that goes back to us being women who are in their 40's and above and it's almost "well they're dead in the water, it doesn't matter".

Patient ?: Maybe there should be a questionnaire saying about each individual and ask them if they can ask them if they can identify themselves with such and such a thing that's going on…we've all

gone through different things haven't we, so there are a lot of people who have gone through that and can't identify that it's a problem.

Patient ? Is the most recent questionnaire, am I right in thinking, because I cocked up filling it in…if you'll pardon the pun…was it the questionnaire that "Are you sexually active now, if no…there were loads of questions that I missed out.

There were 2 parts to it; there was a part for those who are sexually active and a part for those who aren't.

Question 14:

Looking back on the sexual satisfaction point of view; again, there is a lot of evidence to say that people with bladder and prolapse problems have reduced satisfaction with sexual activity, so when we are trying to understand the impact of symptoms on people, we often ask that. What do you feel is the best way to ask about satisfaction of your sex life other than…?

Group: How would you rate your partner on a scale of 1-10? 1 – Diabolically bad!

Patient 3: I think it all depends on your partner as well, how he feels. When I came here she asked me and I said no, because I was scared as well because my prolapse is really bad. My husband does understand, you know, he won't bother me at home. That helps.

Patient 6: I don't think there is any other way to ask it really.

Patient ?: Do you have an enjoyable sex life, if you are sexually active? Does your bladder affect your sex life?

Group: Does it have a negative impact on your sex life.

Do you think the term "Does it have a negative impact on your sex life?" Is that a term that everybody will find comfortable?

Group: No, not for everyone. I thought that was quite good actually. Yes, for me too. It might not be appropriate for all. Do you have as much enjoyment as you did before you had your problem? Does it affect your enjoyment? Enjoy is a good term and I quite like impact because it's a bit sort of…Someone find her a man please. A young doctor…preferably not in gynaecology…a young cardiologist…I should imagine after a day with us women, it would expect a lot of these guys would be gay, there's no way they would find women attractive when they have been looking at that all day long! Do you have many gay gynaecologists? Yeah they say don't they, with a chef, the last thing they want to do is go home and cook.

Patient ?: I remember going to see Professor Cardozo once at her private practice and she had a big chair with stirrups and your bits are on the edge and she just sort of comes towards you. I just went, "Oh my goodness, how do you do this all day?" so she went, "what do you mean, looking up people's fannies?" That just made me laugh!

Patient ?: I think it is down to the dynamics of the individual and there are certain things that…I think "enjoyment"…I think if you want sort of hard facts "impact" and if you were doing clinical study. I think enjoy suits more.

Patient 6: I think as well that it does depend on the individual. What you can say to one person you can't say to another. I mean we can talk quite nicely here, but it is not for everybody. I don't know how you could group everybody in…it's impossible.
Patient ?: It's a bit like how people refer to their vulva/vagina, you know bits. I mean "nunny" is fine if you are four…
Patient ?: I know I shouldn't say this, but because I worked with the elderly, I used to go to a couple who were 89 and 90 and he said, "Bit of sex in my life at the moment" not sexual, they would pleasure each other in different ways and he said he enjoyed it much more than when they were young.

Do you know, I was doing a literature search this morning and sexual activity in later life; for men, it reduces the risk of heart disease and helps you live longer and from a psychological point of view; if you maintain some sexual intimacy, that doesn't mean have intercourse, just have sexual intimacy, reduces depression, improves well-being and anxiety and gives a feeling of secureness and comfort.

Group: My husband is like that, he will be happy. That's why I think it's so important, because it's all linked into emotional well-being. Maybe that's why so many people have got anxiety and depression, maybe. But it's got to be with the right person.

We have covered a huge amount this afternoon ladies, thank you. We have looked at the gender and the age of the person who is having the conversation. We have looked at types of questioning. We have looked at how to introduce and how to always buffer the question to make it less blunt and more open. We have looked at opening up the questions. Talking about medications; partners and we have looked at honesty within the questions and answers.

Does anyone have any other burning comments that they think will be useful to us to ensure that our approach to women about sexual activity and function really improves.

Group: I don't think there is anything else you can say really. There is no other way you can put it. I just think that it's just really good that you are focusing on it, rather than just pushing it under the carpet. There's no other way, you've just got to ask. It's got to be done in a dignified way. In all the years I've been coming to her, it has been.

I know I'm fabulous, but what about the rest of them?

Group: Some of them go in a bit too…I've never come across it. You just sit there quietly, talk quietly.

Don't leave the doors open…don't shout across the waiting room.

Patient ?: That's an interesting point…that the whole thing around sex…you know how sometimes, I would imagine, as somebody leaves that they sometimes might think…"oh well actually"…and it's making sure perhaps that the sex doesn't come last down on the questionnaire, it's in the middle, so there's not that thing about, "oh, just before we finish…" however you decide to ask the question, because otherwise it makes it look like it's a bit peripheral and it's one of those out of the door things.

I don't really want to discuss this, so let me just ask you a quick question before you go.

Do you have the tick now…oh okay!

Patient ? Don't say, "We've got 10 students with us today, do you mind if they sit in".
Patient ? You made a point though, your son being a doctor, that young doctor's do need to learn.
Patient ? I thought, let me ask him, because he is in Portsmouth, so I said it is a very long waiting list here can I come down there. He said it was the same there. He asked me how long I have had this thing and I told him after December, it just came out of nowhere. I had to see the doctor. I felt comfortable talking to him. Even when I came to see Dr Jo I was happy. It was okay, whatever she had to ask, she had to ask, because it's for your benefit.

Group: But not everyone thinks like that. I don't think anyone would think that a doctor or nurse was being nosey though. When she asked me about sex, I wasn't bothered. Just because of periods, having your smear test and everything, women are a bit more, you know.

Patient ?: Doctors do need to learn. I think perhaps, out of all us women; you would know who it would be appropriate to say "would you mind if this doctor sat in and asked a few questions". I'm not saying everybody, but maybe someone who has already answered some questions and if you know that they are alright doing it and you have a doctor who is training, perhaps you could say "would you mind, we have a doctor who is training, would you mind if they sat in on our appointment and ask you some questions?" and I think the majority of women who are comfortable to talk probably wouldn't have an issue with that.
Patient ?: If you redesigning things, would there be any facility, feedback is too formal a term, but if someone did have a conversation and they were left a bit uncomfortable, or they felt that the conversation wasn't…so for the younger doctors that are going through their paces pre-consultant, or even consultant, so that there was some way to refine their approach.

That's an interesting idea.

Patient ?: I think they would need someone, for instance like yourself, they should perhaps sit in with someone like yourself asking the questions, to see how it's done.
Patient ? But then also would there be some facility for, let's say women had been asked about things, but how it could be done better if something was implemented.

In their training they have something where someone pretends to be the patient and they give feedback on their history taking, but that's only in their training.

Patient ?: If you were implementing something within the Trust, maybe a pilot scheme, that might be something to consider.
Patient ?: I wouldn't be happy telling a 25 year old, I would be embarrassed. I would blush. I would be embarrassed.

Group: Then you are not going to get the answers you want. Make them go through the questions; make them be the other person so they know what it's like. As part of training, I think that would be valuable, because they would know that it is uncomfortable. They could think how their mum's would feel. Kid's this age, they know everything. When you get angry, they say you're having one of those days. Do men have a lot of sexual problems?

Yes…erectile dysfunction.
Thank you all so much for chatting and opening up.

Angela Rantell
Lead Nurse, Urogynaecology
PhD Researcher

Introductions

Ladies in the group; I am going to ask you lots of different questions and ask you for comments on them. I am going to start you off with a big question, just to ease you in gently.

Question 1:
When you come to a Gynaecology clinic, do you think it is appropriate for us to ask you about sexual function and sexual activity?

Patient 2: Yes, I don't have a partner at the moment, but one of my concerns with the next one is I am embarrassed, whereas my old partner didn't care because he knew. If I get nervous I need to for a pee, so I want to go pee before sex and then I want to go straight after, because I don't want to get an infection, so yes, I think this is important.

Patient 1: As long as it is a female consultant, I would feel more comfortable.

Patient 6: I agree with you…that was my first thought, I prefer to have a female to talk to.

Patient 5: Yes, I am absolutely fine with that as well. I think you may encounter different views and possibly different age groups. I think the younger people might be more open to talk about that sort of thing, possibly.

Patient 3: It does not bother me whoever, if it is a male or female. With a female I would feel better, but I would not worry if it was a male.

Patient 1: Maybe putting it in the letter that goes out to the patient that this is what is going to take place, so that the patient is mentally prepared for the questions that they can ask, because sometimes you go into an appointment you are not aware of what you can or can't ask. If they ask you when you are there or they ask you at the end if you have got any more questions, you may be embarrassed or you can't remember at the time.

Question 2:
So apart from the possibility of a questionnaire, how else do you think we should approach the topic when we are chatting to you?

Patient 6: I have written something out as I am not very articulate. It's not terribly long, it just happens to be my view. This is the Consultant…It must be very difficult to share with everyone; I am so glad that you have come to me. Forget about your nerves; I am just delighted that you are giving me the opportunity to possibly use my knowledge …?... many years experiencing this problem. If at any point you feel that you are uncomfortable during our chat, just stop; I won't be at all offended; I

am so pleased that at least you have taken the first step on the way to request help. Take as long as you like before answering. The first question is "How long have …? Do you recall how far back this began? Now, after all this time, how does it make you feel? More delicately, you intimate relationship; have you been able to discuss this with your partner? How are you coping? (making a joke of it…avoidance) How does it make you feel about yourself … does it make you feel at ease? What would make you better within yourself? How do you feel now that you have opened up to me? I would love to see you again. Think carefully about our discussion and take care.

So you were the Healthcare Professional, that's the sort of thing you would say?

Patient 6: That's how I would go about it, yes.

Are there any other ways that you think it would be best to be asked, or any ways and any other approach that you think is useful? Anything, so a questionnaire or having it in a letter or being sent a questionnaire beforehand to say "do you want to speak about this; do you have any problems". What are your views on something like that?

Patient 5: I think a questionnaire would be good, possibly asking to tick the box if you would be happy to discuss those matters and I think that takes out the awkwardness for both parts really, when you actually get to the appointment.

Question 3:

For women who aren't currently sexually active, do you think that we should be probing deeper as to why they are not sexually active, or how far within the questions about your sexual activity do you think it is appropriate for us to ask you?

Patient 5: Only if it is related to the problems that certain patient has really. You have to know that patients background to make that question relative, otherwise you could be probing too deep.

Patient 1: Or, as you said, if it is on the questionnaire, then that patient has the option if they want to discuss it. Maybe putting it in the questionnaire puts the onus on the patient if they want to discuss it any further.

Patient 6: I think if you are not going to discuss it, I don't really know why you are there.

Because you'd still have a discussion about your bladder symptoms; this is only talking about your sexual dysfunction on top of that.

Patient 2: I'm not in a relationship at the minute, but I know when I was with my ex, we were discussing my bladder infections and I felt quite comfortable with it. It puts me off now thinking, touch wood, I have not had any bladder infections this year. I mean at one point I was on antibiotics for a year and then stopped them and since I have been single it's a lot better. So for me, the sexual bit does worry me, because, I don't know, is it because they just bruise me and I get infections. Is it in my mind and then I get an infection because I get nervous. I think it is quite relevant and it has put me off…I'm quite happy being single at the minute, but I know if someone comes along I don't want to think "I can't go there because I have an overactive bladder", so I think it's quite relevant.

And what would you like someone to ask you to try and find out that information? How would you like them to phrase it?

Patient 2: I think the questionnaire bit, to give a multiple choice, but also a comments box, because sometimes what I hate with hospital things, I think "well I'm A&B but I'm not that". So just to be able to put a comment, because once I know you have read that, it's easier for me to talk about it, rather than me to sit there and bring it up.

Patient 6: That's a very important issue, the fact that you are left to comment when you are between two.

Patient 1: Also, you have got the time to think about it, rather than being under pressure and not remembering. If you have the questionnaire beforehand you can think about what are my issues and like number 2 said, you can put things in the comments.

Patient 2: If you've put it there, even if you don't bring it up, the doctor has read it and they ask you a direct question, you don't tend to lie then; but if they don't say anything, then you don't say anything, but if they know and they probe on that, they have raised it and they show they are interested then. Sometimes, I've said it to you, I always see a different person here and I feel like no-one cares, because every time I've seen a guy before you, they would all read my notes and go through all the things and go off and I just think "am I just a number". So coming on this, I see you or the other lady and I know where I am and usually it's literally like they are just reading it in front of me and then asking me to repeat my symptoms and then if I said anything different, off they would go and then they would come back and I found it really frustrating.

So you find the familiarity of the person you are seeing actually helps you to open up more.

Patient 1: I don't so much mind, as long as what I put on paper and then they can relate it back to me, I'll put my feelings down on paper, as I am too embarrassed to bring it up in the session, but if it is already on paper, then they can broach the subject for you and ask you more probing questions around it.

Question 4:

When it comes to the actual person asking and I know some of you have made comments about it being women, now is it any woman clinician, so Doctor, Nurse, Physiotherapist; is it a specific group of, Consultant or Doctor, or something like that?

Patient 2: It's any I think.

Question 5:

Are there any other attributes of that Healthcare Professional that you want them to have to make you feel safe enough to open up about things?

Patient ?4: I think I would like them to be a little bit ?approachable.

Patient 6: I would prefer to know that they had read my notes before actually I'm sitting in front of them so that they know me before I come to see them.

Patient 2: I think that before I started this group, that was one of my pet hates here. I think I have seen Dr Cardozo as many as maybe three times. I have seen you a lot. But before you, I have seen different boys; and they were boys; I'm not saying I'm that old, but they were and they were just…I would just come in after waiting about ½ hour and they were just reading it in front of me. I felt that I was a number. If I could have just changed, I would have, but I know Cardozo's brilliant and that's the reason I didn't change, because of her. If I got a different person every week I wouldn't like it.

Question 6:

Do you think age is important in the person who is asking the questions? Do you think that the way that they explain things…any of those factors important when they are checking to you about it?

Patient 2: No, just as long as they are experienced and know what they are talking about, then that makes me feel confident.

Patient 6: I'm 75...

You don't look it!

Patient 6: I am and I wouldn't like to be confronted by a 23-year-old, I would feel very awkward.

Patient 5: That's what I was saying earlier. I think that the younger you are, possibly the more open you are…well not open, but the more confident you might feel. It would not bother me how old the person was, as long as they knew my case.

Patient 6: Because of my age, years ago we didn't talk about things like this.

So that actually brings us nicely into…there is research that has been done across the UK over the past 30 years. It's called the Natsal study and it looks at changes in sexual practice over the years. So they started asking a group of women 30 years ago, questions about their sexual activity and they have repeated it and I think it is around 10,000 men and women and looked at the change in sexual practices. So from 30 years ago to now, women are having more sexual partners than they used to; they are having more same-sex relationships; they are masturbating more than they used to and they are having less vaginal sex and more types of other sex, be that oral, anal, that sort of thing. So when we are coming to try and understand sexual practices, obviously, we need to understand more in depth about exactly what type of sexual practices.

Question 7:

So what is your opinion about asking you questions more in depth about the type of sexual activity you are having and the type of partners you are having that with? How do you feel about that?

Patient 5: I think the more you know about us and what we are doing, the more you are able to help us, but again, it comes to having something beforehand, when you write to us, to ask us if we are willing to talk about this.

Patient 2: For me, anal does not rock my boat in any way, but I know that a lot of people half my age, it's all the rage for them. I think you just do a number 2 out of that end, personally, but each to their own. If you do the questionnaire, for me that will be easy because I'll just skip that or put n/a; rather than if you say to me "do you have anal" I would still say "no".

So you would rather fill that in in a questionnaire rather than be asked about it?

Patient 2: Definitely.

Patient 1: I would much prefer everything to be on my questionnaire; I can be as honest as I want to; skip what I want to; put in what I want to and it is all done on paper and I don't have to feel embarrassed or offended at my actual appointment.

Patient 3: I wouldn't mind being asked when I go to the clinic; "are you having any sex" but yeah, I think that crosses the line…goes to the next level. I feel that the person asking you…it is very hard to not feel awkward and you can see that.

Group: If someone you don't know asks "do you do anal?"

You would be amazed…

Patient 1: You could even put in the questionnaire, are they happy to discuss it further. Maybe we are happy to put it on a questionnaire, but we don't want to discuss it at the appointment; or maybe they are quite free and will have a discussion about what they do, what they use and who they do it with. So maybe to have a really in depth questionnaire would be quite good.

Patient 3: I suppose it's actually having those; it might be someone who is not having a problem with it, they might think it's irrelevant.

Patient 2: I think that if you are having anal, you are really likely to have bladder infections. I think it would be quite relevant. Maybe that's even one of the reasons why it's just not my bag anyway. If it was, that would put me off straight away, because I don't think it's hygienic, personally.

That is why we ask certain women, because for women get recurrent e-coli infections; that and wearing thongs are often the two most common reasons as to why it happens. So in order for us to be able to educate and advice on good practices…

Patient 1: But it could be something that you put into a leaflet that covers all of these subjects, so that if they didn't discuss it with you, but they ticked it, at least they could go home and read up about it.

Question 8:

If, when you are in a consultation and someone doesn't ask you, or there isn't an information leaflet, no questionnaire to fill out beforehand; if you had a problem that was impacting on your sex-life, or your bladder symptoms were a problem or causing problems, would you actually volunteer it to the Healthcare Professional you were seeing and if you were to volunteer it, how would you introduce the subject?

Patient 2: When I was in my last long-term relationship, I did voice that, but before I was coming here, I went to see my GP and I specifically asked for a woman, because I felt uncomfortable. I kept on getting bladder infections, cystitis, thrush and then it put me off and I said that I was with this man for about 5 years and I wasn't going to not have sex; they gave me an antibiotic to take before sex, which would prevent it; now, if I hadn't brought that up I never would have known that and it would have kept happening, so I did; but I couldn't just walk into a room and say, this is what's happening. I had to build up the courage, go to a woman and then say what was happening and as I say, I have got that antibiotic now.

Patient 1: I think, because of the "Embarrassing Bodies", whatever is a problem to me, I now do go and talk to my doctor about it; but before Embarrassing Bodies, I probably would have kept it to myself; I would just struggle my way through it, unless it was really impacting on my life; but because of Embarrassing Bodies, I talk about things now.

Group: Sorry, but I can't watch that. I can't watch it either. I'm embarrassed to watch. I'm embarrassed for the patient.

Question 9:

Is it something that you would, when you are speaking to a Healthcare Professional, is it that you go there directly with that specific issue or is it that you talk about something else and work your way into it? Is that a conversation opener for you or…

Patient 2: For me, I hate going to the doctors and I work, I never have time, I hate waiting. I want to get straight there and I want to be in and out. I've requested either Dr Abraham or Dr ?, he understands.

Patient 6: I'm not wasting time; I'm there for that purpose.

Question 10:

Is there anything about the clinical environment that makes you less willing to open up about things; is it when you are in certain clinic spaces, or if there are other people in the room, medical students or anything like that?

Patient 2: I don't like that; even here, when I had one procedure, they asked; I feel uncomfortable, I have my legs in the sling and I suppose I do feel uncomfortable. If I've got a man; I haven't given birth; I haven't gone through childbirth; I don't even like smears. I certainly don't want a room full of people. If I'm knocked out unconscious you can do what you want, but when I'm there and I'm fully aware…

Patient 5: I've had 3 kids…I'm not bothered whatever, but everyone's different.

Patient 1: I don't mind. At my last appointment there was a student there and in actual fact it was good, because she was thoroughly explaining everything to the student, so it meant that I could kind of understand in layman's terms. I don't mind; I just don't want too many people; if it was like a bunch of Consultants, then I wouldn't be happy, but one or two people, I don't want it to be in a cubicle, it's got to be in a room.

Question 11:

When we are looking at the consultation that you have with us as a whole, is there any point where…what point should we be bringing it up? Is it at the start of the conversation? Should we look at something else first? Should it be towards the end of the consultation? Where would you want it to be?

Patient 2: I think what number 1 said; when we get that letter, you should have that in there; you know, the tick boxes, so once that's in there, we turn up for the appointment, we feel comfortable because we've given you the answers and you can go from there. So I think if that went out in the first place, that's your answer straight away. Whereas, if you just go in and you ask about that I might think, ? , but if you do that questionnaire thing, I think that answers it straight away.

Patient 6: I agree with number 2. With that questionnaire, if you left a big gap at the bottom where you could make your own, real comments; not just on the side; you could really say what your problem is.

Patient 3: I would be quite happy to be asked as part of the symptoms in the consultation. When you go there they usually say "do you have this, this, this". It could slot in as a symptom as well and that kind of normalises it. It kind of puts it in with everything else rather than being a special part of the problem.

Patient 2: I do think that, it's not just urinary, but with a lot of things; when doctors do that; at the minute they are going on about my blood pressure and they start asking me do I have all these symptoms and I think, yeah I do, or no I don't and I think if I had wrote it in that questionnaire first, it is almost like now, I go home and I think, what have I missed. I think that there can be the error that people put these things in your head that you didn't even know and then you suddenly question do I have this, do I have that. So I believe in that questionnaire.

Patient 1: I leave it to the Consultant whenever they bring it up; as long as they have brought it up, I do want them to address it, I don't mind if it's at the beginning or the end; as long as they do address it and I have the opportunity to voice my concerns.

Question 12:

When you are asked about it and when you have the opportunity to voice those concerns, what is it you want back from the clinician; what is it that you are hoping that they will give back to you once you've voiced those concerns?

Patient 2: As I said, when I was with my partner and I got the antibiotics before sex, I want an answer; I'm quite an impatient person and sometimes I expect you to fix it because I've said it, just like that. I know that's realistic and even with my bladder tablets and trial and error, the first one put me in hospital for the weekend here, because my belly distended. It put me off and I wouldn't take another one and then I'm on a different one now. I just want it fixed. That's the only thing and I think it's the same for everyone. They don't like having to try and find a medicine that suits, because you have to wait so long to get into your next appointment and at that same time it's impacting on your life. I just want an answer. I would, in an ideal world, like to be given two different tablets and say, look try that one and if it doesn't work in a couple of days you can swap it

for that one; instead of having to wait, make another appointment, come back and then go on the next one.

Patient 1: I would like options; so maybe it's just the leaflet you can go with, injection or maybe tablets and I want to know what are my options and as number 2 said, I want to come away with something, I don't want them to say "well there's nothing I can do". I do want some sort of answers that I feel that it was not a waste of an appointment and that my needs have been met at my appointment.

Patient 6: I feel I want them to get into my soul and know what I need and know that they understand what I'm feeling and advise me, or at least talk about it; even if they can't do anything, talk to me about it.

Patient 2: I agree with that; I'm so fed up of feeling that no-one feels what I'm feeling, then you've suddenly got my discomfort; because when you are there with some of the young guys and I'm in tears, I just feel so awful that I just want the ground to swallow me up and this young guy, you can see he's dying, he will get up and talk to someone and come back and I just feel that I've wasted all this time in an appointment with a student who didn't know and didn't have any understanding of what I felt like, so again it goes back to the familiarity with people. I think consistency with who you see is a really big part.

Patient 5: I would like some information; whether it's a leaflet or a website you could refer me to, to give me some time to read up about it myself as well. Something like that really, so that I could actually read; take it in; take it on board.

Patient 2: Your leaflet, because I've convinced myself I've got everything in the world on the internet.

Question 13:

When you are having these conversations, what sort of time do you want to…you know, with GP's, sometimes you get 10 minute consultations, how do you think those conversations fit into them?

Patient 2: With my GP, if I know they are 10 minutes I have to book a double appointment; I can't do it in 10 minutes. I have also before, went to the walk-in centre at St Thomas' and they referred me to a doctor and they gave me antibiotics straight away. So I do find that a struggle; they are like, if you can't take the day off work you aren't that ill; I didn't say I was dying, I just said I was infected and it is really impacting my life and I don't know if I'm going to make it to work; you know without getting off to find a toilet; I've squat behind a car; before I had all my tablets and everything, touch wood, I don't have any of this now, but they don't realise the impact.

So when you are chatting to a doctor or nurse in a clinic, what makes you feel like they are rushing you or they are not giving you the time to actually address your concerns?

Patient 2: My doctor, not here, they have told me before "you are only here for one thing, we've got 10 minutes". They have said that to me, so if I've gone "can I have something for my eczema" and then I say "and can" they say no, one thing, you've got a 10 minute appointment, you need to book a double appointment if you want anything else.

Patient 6: You are talking about one thing, but often things are related; even if it's urinary, it can be partially to something else and they can't put it all together.

Patient 1: Maybe they can ask you at the time of booking your appointment how long you think you want; 10 minute or 20 minute; maybe you have something simple that you just need 10 minutes; but maybe you do have more or you are a person who likes to talk and have that interaction so you will need longer.

So is that just in your GP practices, or has anyone had any experience of that here?

Group: I haven't really been rushed, not here or at my GP. Not here.

Patient 2: For me, it's very much at my GP. I have told Dr Abraham that if it wasn't for him, I would leave the surgery and find another one. I don't think it happens so much at the hospital because you schedule your appointments and you pretty much stick to them, unless there's an emergency. That's the way it is here anyway, which is why I didn't opt to ever change, even though I never saw Dr Cardozo.

Patient 5: I've never felt rushed here. To be fair, I don't think I've ever felt rushed at my GP. Sometimes I feel that they don't listen to me, or they don't have the time to listen to me, but I very rarely go to my GP and if I do, I go in to say please can you just refer me back to Kings. As long as I know what I need and thankfully, touch wood, so far I have done so as long as I stay on top of it. Here I have always had fantastic service.

Patient 1: I usually go in with a list of points that I want to discuss and questions that I want answering. I've never felt rushed at the end.

Patient 2: I did get approached by, I was here one day and I said no. It was that TV programme here, 24 hours in A&E and I had come with a bladder infection and that's an embarrassing thing anyway. They came up and I'm not being funny or bigging myself up, they said I looked like the only normal person in A&E at 3am, because I just can't go through the night and the camera people came and I said no just please go away and then other people were treating it like it was a celebrity thing.

I think, one of the things that we always say in clinic is that we may run late and you may have to wait longer in the waiting room for the appointment, but it's because we won't rush anyone out and give people the time to they need to talk, because they don't get it at their GP's, so we'd rather give you that time and run a bit late.

Patient 6: I agree, I've never, ever been rushed here, whereas with the GP it's, "you've got 10 minutes, don't discuss anything else".

Patient 5: Actually I had my referral the other day and what I liked about that was I had the option to call them between certain hours or I could e-mail. If I e-mailed, I could put in which date I would like to avoid or which dates I preferred, which really suited me because I had to look through my calendar…it was really nice to have that option.

Patient 2: I haven't seen that option and I want it.

It's only happened in the past few weeks and it's only with physiotherapy at the moment. It's due to the fact that the management of the administration has gone from the Women's department to the Physiotherapy department and the way the appointments are being booked and the waiting list. It's down to this is the new option to try and make it all easier being as it's no longer being booked by our department, so it's gone external. So we are trialling it to see.

Question 14:

When you come to clinic and when we are asking the topic about sexual activity and sexual function; if you have your partner in the clinic room with you, or your friend in the clinic room with you, how do you feel then about us asking the subject, when there is someone else there and do you think it changes the way you are going to talk about it with us?

Patient 2: I wouldn't take them in anyway. I don't know why they need to; whether it was my partner or my friend. I think you can keep the romance alive a little bit; they don't need to know everything. I was with someone for 5 years; if he took me to the hospital, he certainly didn't come to my appointment with me. Maybe if it was a heart attack or something different; he doesn't need to know everything that's going on down there. He needs to look at that and feel good.

Patient 6: I wouldn't dream of bringing my husband.

Patient 1: I would…I wouldn't mind, but I wouldn't have my friend; I wouldn't even have my sister, but my partner.

Group: Have you had kids? Yes with my ex-husband. But I've been told you have no inhibitions when you've had a family. That's what my sister and my family. I don't know really, I think it comes down to the number of medical procedures you've had. It's not just down to children. My partner would probably ask questions. It depends who is in the room with them.

Many women bring someone with them for an appointment, especially if it is their first time coming, because sometimes you don't always remember everything that's said to you and all that information, so having someone else there to keep track of things; but it is that, if it is someone that you are not necessarily, you know, if you had a friend in there, would you open up and be honest about if you were having problems with sexual function and things like that?

Patient 5: I suppose if you've had the questionnaire beforehand and you ticked whatever boxes and been asked whatever questions, then you as the patient would be prepared as to whether or not those questions are going to be asked of you; so if you took that person in, you would know either way.

Patient 2: I think it is how you ask. I am very independent, even when I have been I a relationship; but then I've got other friends who do have partners and they do everything, so I do think that it is relevant to how you are as a couple.

Question 15:

What about if you are going to be sending out a questionnaire to look at this; would you, do you think, take offence to say "if you have a partner with you at the appointment, would you like us to ask them to leave the room before we question you on this?" What do people think about that?

Patient 6: Obviously I wouldn't be offended because I wouldn't take him in.

Patient 3: I suppose I would do is not take them in. If I knew those things were going to come up and I suppose it's good to have something said beforehand so you would know they were going to come up. I suppose what you wouldn't want is to go in unaware and to be asked questions that actually you really want to talk about, but not with them. So if you know in advance what's going to be asked, you can decide who to bring and whether you want to bring them in the room or not. I suppose once they are in, I would find it a bit weird if to ask them to leave.

One of the things that I did before chatting with you ladies, last year, I actually did something similar amongst clinicians, looking at Gynaecologists, Urologists, Obstetricians, Nurses, Physio's, about how they felt about discussing sexual function with patients. If there were people, particular types of people, that they found it more difficult to approach, or to ask questions; how in depth they went and one of the questions was actually around, how honest and open patients actually are with you and if you ask a man or a woman a certain question about their sexual activity, what things do you think they most likely may not be completely honest about. So for example, when they ask "what do you think men may not be honest about", it was generally, well maybe the number of sexual partners they've had; about erection quality; how long they last, were typical the male bravado and stops them necessarily actually truly being honest.

Question 16:

Do you think there are any things that women may not give us the true answers to?

Patient 2: I mean I have no inhibitions so I would say how many sexual partners, but I know a lot of people, even my friends, who lie. I went to school with them; I grew up with them and they are married now and I've been there, you know, when they do truth/dare and they all say "how many partners have you had" and they say three and I think, yeah put a zero on the end…I know. I think women do lie about that just as much, especially for me, I find more so with my married friends. I also think there are misconceptions about what is deemed good and what isn't.

Anyone else any ideas of either what you may have not necessarily been honest about in clinics with us, or things that you think people wouldn't 100% admit to?

Patient 5: Possibly the quality, the enjoyment side of it. Drug taking; that sort of thing.

Patient 2: One of my friends is a Policewoman and you know, I'm in my 40's now. I did so much LSD in my teens and twenties; we all did it together. We are not allowed to speak about it now, it's like she was this completely different person because she married a cop. I'm like, surely you shouldn't be ashamed of what you did 27 years ago; we all grew up; we all did this. If she was still doing it now I would understand, but yes, I do think that people look at appearances and what they perceive; people lie about that.

Patient 5: Casual sex as well.

Why do you think people aren't necessarily honest about those sort of things, if they are having a problem and a Healthcare Professional is asking them a direct question, what do you think is it that motivates them to not tell us?

Patient 5: You're being judged, I suppose.

Patient 2: Their own self-esteem. When you actually say out loud sometimes what you've done, it sounds a lot worse than when you are actually doing it, you know. As you get older, you look at things differently. I have no embarrassment about what I did in my younger years, but I have a lot of friends and colleagues that make out they were saints. To me, I don't understand it, but obviously I respect their wishes and that's how they are. In front of my cop friends, it's like we didn't have that childhood and she won't even acknowledge it or anything.

Patient ?5: Would there be anything about, so say if they are asking you about things that you have done and it might be related to a problem that you now have, obviously you don't want the blame for it, or let's say you keep having these e-coli infections and they ask you "are you having anal" and you say "no!, no!", it's not my fault obviously. I go to my GP and I say, my leg hurts and they say, "well you should stop smoking!". It's that sort of thing.

Patient 2: I agree with that, because some doctors do. I'm an ex-smoker, I quit when I was 25, 20 years now, but sometimes it still winds me up. They ask me the question "do you smoke" I say "no" and they say "have you ever smoked" and I say "yes" and they tick that box as if I've been really naughty. Some GP's and Consultants do come across like that.

Question 17:

Going back to the partner point of view, do you think women are generally open about these things with their partners? Do you think that if the woman has incontinence, do you think the partner always knows, or do you think they hide it?

Patient 2: I think it comes with how comfortable you get with that partner; it's not something you would share straight away. Like I say, it's an inhibition, if I get with a new partner; whereas with my ex, I didn't care. He used to call me the phantom pisser because I used to get up three times in the night and this is before I ever come to Gynae. I lived with him for years and that was a private joke, but now, if I got with a new partner, I probably wouldn't be staying at his until I felt that comfortable.

Patient 6: My husband hasn't a clue that I am terribly incontinent because I avoid sex; it's awful, but I have to wear a pad 24/7 and it's just dripping wet. I avoid it and I sleep right on the side of the bed, but I put it down to, he's got a defibrillator, so I don't want him to die! I don't talk to my partner, I can't.

Patient 1: I'm the opposite; we talk about everything. I'll probably go home this morning and discuss this. I am happy for him to be in the room with me; if I need to go to the loo during sex, we'll stop and I say I need to go, so he completely understands, but it's a long term partner so it's very comfortable. I think if it was someone new, I would be exactly the same as you. I would be embarrassed.

Patient 2: For me, since I've been on Mirabegron, it's improved a lot than it ever was. Without them tablets, I would have nightmares before I would even consider going into a relationship, but the tablets that I do have do make a big difference. I'm not in a sexual relationship at the moment to know, if I was, would I start getting infections again.

Question 18:

So, looking at, you know I'm going to throw out an open question now, because we are coming up towards the end of an hour and I want you to tell me, each individual view on, what for you is the ideal way for you to be introduced to the idea of discussing sexual function and bladder problems and actually have it brought into your treatment? So whether it be having a questionnaire and having someone talk it through; whether it be just having someone ask you a certain way or bring it into the topic; what is your personal ideal way of someone ask you?

Patient 2: Questionnaire and then they bring it in, because I feel that I've already raised it without saying it myself and I'm not embarrassed; then doctors tend to probe then when they read things; do you ever get infections; do you have sex; it's just like a robot to me, whereas if I've wrote things like that, they'll ask what were your symptoms, how often do you have those; they will probe from there. So for me, I think the questionnaire with a multiple choice and a big comment box where I can add my own bits and they've read my notes before I turn up, because that's one thing I've really hated about here, I think that to me would work for pretty much 99% of people. You are always going to have a few that might have trouble with writing and that, so it won't work for them and some people can't express themselves, but number 6 wrote all her words down and she felt quite confident and comfortable, so that whole writing thing would work for them.

Patient 5: I agree with you and I think a big area for comments, but I would like them to be really friendly.

Patient 3: I actually came in for a scan and I didn't need anything further, so for me it was quite a short term visit, so I don't know if I would require all that on a one off or my first visit, but say I was in a situation where I had to come back regularly, I suppose at that stage the questionnaire would be really useful, but I would say that for my initial, potentially not having to come back, just the first one, I think it would be okay just to be asked about it and not go into long thing about it.

Patient ?: I agree, obviously mine is more long-term, so I think a questionnaire, to be able to think about it comfortably.

Patient 1: I agree, I think having the opportunity to think about what is happening to me and being able to document that before I go to my appointment, it's very important. At the appointment, I've probably been having a busy day and I won't remember, or be embarrassed or whatever, but if it's all down on paper, then I know they have all the information and they can ask me questions from there. Having someone who is quite friendly and not too many people in the room and just having a nice environment so that I do feel comfortable to talk about it. Having something to take away with you; a website to look at, a plan of medication or something so that I feel that my appointment was worthwhile and I do feel I have got something from it.

Patient 2: At one point a few years back, this made me quite depressed and I actually did that before going to my doctor because I knew if I went in there, I wouldn't say half the things and once I start crying then I can't get it out anyway, so I wrote down everything I was feeling and they did send me to a counsellor, but it was partly because of this because I felt that I was living on tablets, always going to pee, if I'd been out drinking I would have to get off the tube and I would have to pee behind a car if I knew I could not make it home. Another time I had to get a cab and I said I don't care, pull

over on the bridge, because I knew I couldn't get home and it was only a 10 minute journey, I knew I just couldn't do it. I really got quite depressed.

So a questionnaire is a good idea and it is something we can definitely look at; however, we are in a room with people that are actively helpful towards they are trying to improve things and fill out the questionnaires, but a lot of people don't fill out the questionnaires, either because of problems that they can't read; it's the wrong language or something like that and we can't create something for every single language available; or because people just don't fill out their things before they come and see us. How do you think it's best to get those people?

Patient 6: I think to ask them if they would appreciate a questionnaire or not, because also a lot of people look at a questionnaire like they do filling the form for stickers for the Disabled. It's another task, it's rather clinical, got to get it done, without any emotions they just fill it in. I would like to be asked if I want a questionnaire or not.

Patient 1: If for whatever reason the questionnaire wasn't completed, then the Consultant or Nurse or whoever should know how to the subject.

Patient 2: I didn't realise how many people in their 20's actually can't read and write. I've got a couple that when we've done their payroll forms, they have literally only been able to write their first names, couldn't even write their surname and some of them I know and they will never say and I will do it for them, because they can barely read or write and this is English people as well as Eastern Europeans. I think it's quite shocking in this day and age. I don't originate from London; I've been here for 25 years now, but it seems greater up here than the small little village I come from.

Question 19:

Do you think we should change our approach based on the age of the patient? Do you think I should be asking exactly the same questions that I should be asking a 20-year-old or do you think age is a factor that should make us change our approach to things?

Patient 2: I think you should ask them how they would like to be. We can tailor it to you, or would you feel comfortable if I give you the generic form. I think more that will come into it than age would be religion. I have some Muslim friends; they are not going to answer you no matter what you do. Not all of them; I've got some quite Western ones and some; I don't know what you call the opposite. So I think religion would impact more than age.

Patient 5: I don't think it should be changed for age; I think you could give them the option. Some people won't be confident or happy talking about it and others will.

Patient 1: Maybe explaining the importance; I think if I was in my teens I wouldn't really see the importance of the impact of me coming forward and expressing myself. If it's all explained to us, whether it be in a letter or at our appointment, the importance of what we are doing and why we are doing it and the long term benefits; that would be a good idea as well.

Patient 2: It is how we approach it as well; a totally different thing; I left Guy's Hospital, my orthopaedics, the surgeon said to me after one answer, "well if that didn't work nothing can help you" and then they took me to Dr … and he was brilliant. He said "I'm really sorry you had this

experience", but some of the Consultants, this is what I've encountered; they really live on a different planet.

So the empathy towards the patient

is important. Question 20:

So we have covered a lot. We've covered lots of bits and pieces. Does anybody have any final thoughts of the day? What do you think the most important thing for us to consider is when we are approaching the subject of sex, with women, what do you think are the most important things to ask?

Patient 2: It's all about your tone…how you ask the questions. That will straight away set me at ease or not. As long as I can see that the person does actually care.

Patient 6: I think that is of prime importance, that you are comfortable with the person.

Patient 1: I first saw the Consultant and she was very good, she explained the whole procedure to me. She told me what was going to happen and told me who would be in the room. By the time I had the procedure the nurse was in the room and there were more people, so I think that confidentiality where I could speak openly and comfortably without feeling there were lots of people around was important.

Patient 3: I always think that everything is normalised, otherwise when you get to that part to the consultation, it's just awkward.

I'm going to bring it to an end there ladies. We have had a really good discussion. Thank you for being honest and opening up and giving us opinions, it has been really useful. Hopefully, I'm going to work on getting some things out of this, along with the one I did last week and if you are interested at looking at what we come out with, then please get in touch and I will, once I've written it up, be more than welcome to have a read of it. It probably will be written into a paper that will publish looking at opinions and things like that. This is one chapter of nine…the best chapter obviously.

Thank you.

Additional information from Chapter 7

Table 1. REC submissions since initial favourable opinion

Date	Submission	Notes
14/06/2012	Confirmation of favourable ethical approval	
24/01/2013	Confirmation of minor amendment 1	Change in supply of IMP from trial stock to commercial stock
28/05/2013	Confirmation of substantial amendment 1	Additions of GSTT as a Patient identification centre
26/06/2013	Confirmation of annual progress report	
25/09/2013	Confirmation of substantial amendment 2	Addition of Imperial as a research site
21/05/2014	Confirmation of substantial amendment 3	Addition of Croydon and Medway sites
04/07/2014	Confirmation of annual progress report	
20/11/2014	Confirmation of substantial amendment 4	Change in PI at Medway site
20/07/2015	Confirmation of annual progress report	
05/08/2015	Confirmation of minor amendment 2	Updated SMPC for fesoterodine
25/09/2015	Confirmation of substantial amendment 5	Change to protocol for bladder diary variables and sexual activity inclusion criteria
12/02/2016	Confirmation of substantial amendment 6	Extension of trial until 31/12/2016
26/11/2016	Confirmation of annual progress report	
04/03/2017	Confirmation of end of trial	

Table 2. List of protocol versions throughout the clinical trial

Protocol version	Date	Changes
1	05/11/2009	Put into KHPCTO CTIMP template
1.1	05/05/2010	1.1-1.7 changes as per the KHPCTO prior to submission
1.2	08/11/2010	As above
1.3	01/02/2011	As above
1.4	16/06/2011	As above
1.5	10/06/2011	As above
1.6	13/10/2011	As above
1.7	18/11/2011 (First submitted to ethics)	1.7-1.9 changes as requested by the ethics committee
1.8	06/02/2012	As above
1.9	23/05/2012 (First Approved by ethics)	As above
2.0	24/01/2013	Change in drug supply from trial drug to commercial stock
2.1	01/07/2013	Addition of GSTT as a PIC
2.2	28/08/2013	Addition of Imperial site
2.3	23/12/2013	Addition of Croydon and Medway sites
2.4	17/11/2014	Change in PI at Medway
2.5	17/08/2015	Change to protocol
2.6	23/09/2015	Extension of timeline

Regression Models reported from Chapter 8

In order to determine if SF and QoL outcomes were independent of UDS variables regression models were developed and analysed at week 0 and week 12. UDS variables were not a good predictor of any of the scores on the PISQ-12, SQOL-F or PAC-QOL. The results of the regressions with the KHQ were not significant. All confidence intervals are reported in parentheses.

Regression PISQ at week 0

A regression model was produced to compare the association between urodynamic parameters with PISQ score at week 0, which produced an adjusted R^2 of -0.020. This was associated with a non-significant F-ratio ($F = 0.904$, $p = 0.468$) indicating that this model was not a good predictor of PISQ score. The model parameters are summarised in the table 8.10 below:

Table 8.10 Linear model of predictors of PISQ-12 scores at week 0

	B	**SE B**	***β***	***t***	***p***
Constant	16.35 (-2.17, 34.86)	8.498		1.924	0.159
First Sensation Volume	0.046 (-0.021, 0.112)	0.106	0.03	1.502	0.764
Max Cystometric Capacity	-0.011 (-0.052, 0.031)	0.019	-0.148	-0.566	0.582
Detrusor Contraction Time	-0.774 (-2.488, 0.941)	0.787	-0.35	-0.983	0.345

Regression PISQ at week 12

A regression model was produced to compare the association between the change in urodynamic parameters with a change in PISQ score over the 12 week period, which produced an adjusted R^2 of 0.95. However this was associated with a non-significant F-ratio (F=6.376, p = 0.28), indicating that this model was not a good predictor of a change in PISQ score. The model parameters are summarised in table 8.11.

Table 8.11 Linear model of predictors of change in PISQ-12 scores over 12.

	b	**SE B**	***β***	***t***	***p***
Constant	6.8 (-121.1, 134.7)	10.1		0.678	0.621
First Sensation Volume	0.12 (-1.34, 1.57)	0.12	0.386	1.012	0.496
Max Cystometric Capacity	-0.23 (-1.11,0 .65)	0.07	-1.688	-3.335	0.185
Detrusor Contraction Time	-2.3 (-28.6, 24.0)	2.07	-0.712	-1.114	0.466

Regression SQOL-F at week 0

A regression model was produced to compare urodynamic parameters with SQOL-F score at week 0, which produced an adjusted R^2 of -0.175. This was associated with a non-significant F-ratio (F = 0.254, *p* = 0.857) indicating that this model was not a good predictor of SQOL-F score. The model parameters are summarised in table 8.12.

Table 8.12 Linear model of predictors of SQOL-F scores at week 0.

	b	**SE B**	***β***	***t***	***p***
Constant	68.54 (22.41, 114.66)	21.17		3.237	0.007
First Sensation Volume	-0.065 (-0.231, 0.1)	0.076	-0.33	-0.862	0.406
Max Cystometric Capacity	-0.003 (-0.106,0 .1)	0.047	-0.019	-0.067	0.947
Detrusor Contraction Time	1.35 (-2.922, 5.622)	1.961	0.263	0.689	0.504

Regression SQOL-F at week 12

A regression model was produced looking at the association between the change in urodynamic parameters and a change in SQOL-F score over the 12 week period, which produced an adjusted R^2 of 0.74. However this was associated with a non-significant F-ratio (F=0.959, p = 0.618), indicating that this model was not a good predictor of a change in SQOL-F score. The model parameters are summarised in table 8.13.

Table 8.13 Linear model of predictors of change in SQOL-F scores over 12.

	b	**SE B**	***β***	***t***	***p***
Constant	54.1 (-743.3, 851.5)	62.8		0.862	0.547
First Sensation Volume	-0.94 (-10.02, 8.14)	0.72	-1.144	-1.317	0.414
Max Cystometric Capacity	.99 (-5.37, 5.57)	0.43	0.266	0.23	0.856
Detrusor Contraction Time	-10.17 (-174.39, 154.04)	12.9	-1.146	-0.787	0.576

Regression KHQ at week 0

A regression model was produced to compare urodynamic parameters with KHQ score at week 0, which produced an adjusted R^2 of 0.478. This was associated with an F-ratio (F = 3.358, *p* = 0.059) that approached, but did not reach, significance. This suggests that while the urodynamic parameters included did not produce a good predictive model for KHQ score, there was a marginal trend in this direction. The model parameters are summarised in table 8.14.

Table 8.14 Linear model of predictors of KHQ scores at week 0.

	b	**SE B**	***β***	***T***	***p***
Constant	866.3 (551.2, 1181.4)	143.2		6.05	0.000
First Sensation Volume	-0.158 (-1.292, 0.975)	0.515	-0.093	-0.307	0.764
Max Cystometric Capacity	-0.974 (-1.676, -0.273)	0.319	-0.668	-3.057	0.011
Detrusor Contraction Time	10.69 (-18.86, 40.24)	13.43	0.239	0.796	0.443

Regression KHQ at week 12

A regression model was produced to compare the change in urodynamic parameters with a change in KHQ score over the 12 week period, which produced an adjusted R^2 of 0.94. However this was associated with a non-significant F-ratio (F=5.247, *p* = 0.308), indicating that this model was not a good predictor of a change in KHQ score. The model parameters are summarised in table 8.15.

Table 8.15 Linear model of predictors of change in KHQ scores over 12.

	B	**SE B**	***β***	***t***	***p***
Constant	115.7 (-2563.1, 2794.4)	210.8		0.549	0.681
First Sensation Volume	-2.8 (-33.3, 27.7)	2.4	-0.485	-1.159	0.453
Max Cystometric Capacity	-3.2 (-21.5, 15.2)	1.5	-1.215	-2.189	0.273
Detrusor Contraction Time	-42.1 (-593.8, 509.5)	43.4	-0.680	-0.971	0.510

Regression PAC-QOL at week 0

A regression model was produced to compare urodynamic parameters with PAC-QOL score at week 0, which produced an adjusted R^2 of 0.055. This was associated with a non-significant F-ratio (F = 1.293, *p* = 0.322), indicating that this model was not a good predictor of PAC-QOL score. The model parameters are summarised in table 8.16.

Table 8.16 Linear model of predictors of PAC-QOL scores at week 0.

	b	**SE B**	***β***	***T***	***p***
Constant	74 (9.58, 138.42)	29.57		2.503	0.028
First Sensation Volume	-0.105 (-0.336, 0.126)	0.106	-0.341	-0.993	0.764
Max Cystometric Capacity	-0.974 (-1.676, -0.273)	0.319	-0.668	-3.057	0.34
Detrusor Contraction Time	3.072 (-2.893, 9.038)	2.738	0.384	1.122	0.284

Regression PACQOL at week 12

A regression model was produced to compare the change in urodynamic parameters with a change in PAC-QOL score over the 12 week period, which produced an adjusted R^2 of 0.95. However this was associated with a non-significant F-ratio (F=6.467, *p* = 0.28), indicating that this model was not a good predictor of a change in PAC-QOL score. The model parameters are summarised in table 8.17 below:

Table 8.17 Linear model of predictors of change in PAC-QOL scores over 12 weeks.

	b	**SE B**	***β***	***t***	***p***
Constant	19.2 (-396.9, 435.3)	37.8		.586	0.662
First Sensation Volume	-.97 (-5.7, 3.8)	0.37	-0.985	-2.601	0.234
Max Cystometric Capacity	.34 (-2.5, 3.2)	0.23	0.767	1.525	0.273
Detrusor Contraction Time	5.5 (-80.2, 91.2)	6.7	0.520	0.819	0.563

Chapter 12 - Full Results

Results

Four hundred questionnaires were completed over 9 months. This does not represent all the women attending the UDS clinic. Twenty two women refused to complete the questionnaires because they did not feel it was appropriate or did not want to discuss the subject. Some women were unable to read or write in English and although the PISQ-IR is available in different languages it was decided not to further investigate this group as they would not have been suitable for the main trial. A further group of approximately 50 women 'forgot' to complete or return the questionnaires at their appointment. This is not uncommon in routine clinical practice. Table 11.1 displays the presenting complaints of the women who completed the questionnaires.

Table 12.1 Presenting complaints of Group 1

Complaint	Number of women (%)
Urinary Incontinence (UI)	193 (48)
Pelvic Organ Prolapse (POP)	34 (9)
LUTS and POP	117 (29)
Other (eg recurrent UTI, voiding difficulties)	56 (14)

Group 1

Of the women assessed, two hundred and thirty two (58%) were SA and one hundred and sixty eight (42%) were NSA.

Three hundred and sixty three women went on to have a full urodynamic assessment. There was minimal difference in SA activity between the different UDS diagnoses as shown in Table 11.2. UDS were not performed if the patient had a symptomatic UTI or if it was felt to be unnecessary for their further management.

Table 12.2 Sexual activity according to UDS diagnosis

Urodynamic Finding	**N**	**% SA**	**% NSA**
Test not performed	37	35	65
Normal	128	55	45
Mild urodynamic stress incontinence	35	68	32
Moderate urodynamic stress incontinence	30	60	40
Severe urodynamic stress incontinence	20	75	25
All urodynamic stress incontinence	85	67	33
Detrusor overactivity	95	60	40
Voiding difficulties	4	50	50
Low capacity	26	62	38
Urodynamic mixed incontinence	21	70	30

Eighty nine women (53%) of the NSA women were NSA because of lack of a partner. When the 79 women who were NSA but had a partner were

asked to consider the reasons as to why they were not SA, 60% reported that this was secondary to their bladder symptoms, 45% due to other health problems, 53% reported having no interest and 58% were bothered ‘A lot’ by their lack of sexual activity.

Group 2

Ninety five women were found to have DO on UDS. Of these, 60% (n=57) were SA. Of the SA women 93% (n=53) reported UI compared to 100% of the NSA women.

For 47% (n=18) of the NSA group, lack of a partner was cited as why they were not SA.

Only 9 women reported having a partner and the other women did not answer. When the 9 women who were NSA but had a partner were asked to consider the reasons why they were NSA only 33% (n=3) reported that this was secondary to their bladder symptoms, 55% (n=5) due to other health problems, 67% (n=6) reported having no interest and only one woman was bothered ‘A lot’ by her sexual status.

Group 3

Sixty seven women reported symptoms of OAB but had normal UDS findings. Of these only 45% (n=30) were SA. Of the SA women 87% (n=26) complained of OAB wet compared to 70% (n=26) of the women who were NSA.

65% (n=22) were NSA because of lack of a partner. Only 6 women reported having a partner and the other women did not answer. When the 6 women who were NSA but had a partner were asked to consider the reasons as to why they were NSA 67% (n=4) reported that this was secondary to their bladder symptoms, 83% (n=5) due to other health problems, 83% (n=5) reported having no interest and 50% (n=3) were bothered ‘A lot’ by their sexual status.

The differences in baseline characteristics between the three groups is presented in table 11.3. The differences in rationale for sexual inactivity between the three groups is demonstrated in table 11.4

Table 12.3 The differences in baseline characteristics between the three groups.

	N	Mean age (years)	Median parity	Sexually Active	Not Sexually Active	Concomitant POP + LUTS
Group 1	363	45.06	2	58%	42%	38%
Group 2	95	49.74	2	60%	40%	32%
Group 3	67	49.65	2	45%	55%	37%

Table 12.4. The differences in rationale for sexual inactivity between the three groups

Group	**N=**	**Sexually active**	**Not sexually active**				
			Lack of partner	**With a partner**			
				Due to bladder problem	Due to other health condition	No interest	Bothered 'a lot' by sexual status
1	363	58%	53%	60%	45%	53%	58%
2	95	60%	47%	33%	55%	67%	11%
3	67	45%	65%	67%	83%	83%	50%

Comparisons of the SA and NSA populations

Several analyses were performed to attempt to compare the SA population to the NSA population in each group.

Group 1

To investigate factors such as age, parity, UDS diagnosis, associated faecal incontinence that would make someone more likely to be SA than NSA, a binary logistic regression was used. The odds ratio for the UDS categories compared the observed category to the category "No active diagnosis" (NAD). The model was not statistically significant $\chi 2(8) = 8.838$, $p = 0.356$. It explained 2.9% of the variance in sexual activity and correctly assigned 61.0% of cases. None of the covariates examined made a significant contribution to determining whether our subjects were sexually active or not. No multicollinearity was identified between the variables (Tolerance >> 0.1 and VIF <<10).

The model parameters are displayed in the table 11.5.

Table 12.5 Binary logistic regression for factors influencing SA

	B	**S.E.**	**Wald**	**df**	**Sig.**	**Odds Ratio**	**95% C.I.for EXP(B)**	
							Lower	Upper
Parity	-.413	.301	1.875	1	.171	.662	.367	1.195
POP	.028	.246	.013	1	.908	1.029	.636	1.665
UI	.079	.310	.064	1	.800	1.082	.589	1.988
FI	-.651	.632	1.062	1	.303	.522	.151	1.799
USI	.521	.316	2.717	1	.099	1.684	.906	3.131
DO	.139	.301	.213	1	.644	1.149	.637	2.073
VD	-.302	.737	.168	1	.682	.740	.175	3.134
CAP	.271	.462	.343	1	.558	1.311	.530	3.243
Mixed	.859	.537	2.560	1	.110	2.361	.824	6.760
Constant	.448	.312	2.068	1	.150	1.565		

POP – pelvic organ prolapse, UI – urinary incontinence, FI – Faecal incontinence, USI – urodynamic stress incontinence, DO – detrusor overacitivty, VD- voising difficulties, CAP – low capacity bladder, Mixed – mixed urinary incontinence

The relationships between sexual activity and feelings of frustration, inferiority and anger about levels of sexual activity were analysed using Pearson's Chi square test, which looks for differences between the observed and expected numbers of participants in each category (We compared the answers to Q5 a,b and c to Q20 a,b and d to determine if women who are NSA are more frustrated / angry that those who are SA).

Group 1

There was no significant relationship between feelings of frustration ($\chi2(1) = 0.54$, $p = 0.822$), inferiority ($\chi2(1) = 1.125$, $p = 0.315$), or anger ($\chi2(1) = 0.120$, $p = 0.737$) and sexual activity.

Group 2

There was no significant relationship between feelings of frustration ($\chi2(1) = 0.145$, $p = 0.703$), inferiority ($\chi2(1) = 0.321$, $p = 0.517$), or anger ($\chi2(1) = 0.187$, $p = 0.665$) and sexual activity.

Group 3

There was no significant relationship between feelings of frustration ($\chi2(1) = 2.911$, $p = 0.088$), inferiority ($\chi2(1) = 1.609$, $p = 0.205$), or anger ($\chi2(1) = 0.001$, $p = 0.977$) and sexual activity.

To further investigate feelings of anger and frustration in the SA group, the patients were broken down into smaller groups according to their presenting complaint of either UI, POP or both. Although, women with UI or POP reported similar levels of anger and frustrations, it was the women with UI

and POP who were the most frustrated and angry with the impact that their condition has on their sex life. This is demonstrated in table 11.6.

Table 12.6 Breakdown of frustration and anger in the SA group according to presenting complaint in comparison to the NSA population (Group 1)

Question	Urinary Incontinence (UI) alone (%) (N=112)			Pelvic organ Prolapse (POP) Alone (%) (N=17)			UI and POP (%) (N=89)			Not Sexually Active (%) (N=168)		
	A	D	U	A	D	U	A	D	U	A	D	U
I feel frustrated by my sex life	43	52	5	35	59	6	61	36	3	38	38	24
I feel angry because of the impact that UI/POP has on my sex life	42	53	5	47	47	6	57	39	4	31	38	26

A= agree, D= disagree, U= unanswered

The relationship between sexual status and avoiding/restricting sexual activity through fear of leaking urine and/or stool and/or a bulging in the vagina was analysed using Pearson's Chi square test, which looks for differences between the observed and expected numbers of participants in each category.

Group 1

In the SA population, 38% of women reported sometimes / usually or always leaking urine with any type of SA and 66% state that fear of leakage caused them to avoid SA at times. In the NSA population 48% reported that the fear of leakage caused them to avoid or restrict SA yet 45% of these women did not have a partner.

The Chi square test showed that fear was not associated with any differences in sexual behaviour between the two groups ($\chi2(1) = 3.426$, $p = 0.064$).

Group 2

In the SA population, 39% (n=22) of women reported sometimes / usually or always leaking urine with any type of SA and 61% (n=35) stated that fear of leakage caused them to avoid SA at times. In the NSA population 55% (n=21) reported that the fear of leakage caused them to avoid or restrict SA yet 81% (n=17) of these women did not have a partner.

The chi square test showed that this fear was not associated with any differences in sexual behaviour between the two groups ($\chi2(1) = 0.44$, $p = 0.833$).

Group 3

In the SA population, 47% (n=14) of women reported sometimes / usually or always leaking urine with any type of SA and 73% (n=22) stated that fear of leakage caused them to avoid SA at times. In the NSA population 43% (n=16) reported that the fear of leakage caused them to avoid or restrict SA yet 75% (n=12) of these women did not have a partner.

The chi square test showed that this fear was not associated with any differences in sexual behaviour between the two groups ($\chi2(1) = 3.337$, $p = 0.068$).

Assessment of the NSA population

A detailed analysis of the NSA group was performed to try to explore factors that could influence reasons for sexual inactivity such as age, parity, UDS diagnosis.

Group 1

A Binary logistic regression was used to investigate the relationship between each part of Question 2 and Question 3 and covariates among the NSA group. The odds ratio for the UDS categories compared the observed category against the category NAD. No multicollinearity was identified between the variables (Tolerance >> 0.1 and VIF <<10) :-

Q2a (No partner)

The model was not statistically significant $\chi2(7) = 5.678$, $p = 0.578$.

Q2b (no interest)

The model was not statistically significant $\chi2(7) = 9.158$, $p = 0.242$.

Q2c (due to bladder / bowel problems)

The model was not statistically significant $\chi2(7) = 15.691$, $p = 0.028$. It explained 20.1% of the variance in sexual activity correctly assigned 63.3% of cases. None of the covariates examined made a significant contribution, however, trends were noted that the older the woman, the more likely she was not have sex due to UI/FI/POP, but increasing parity appeared to counteract this.

Q2d (other health problems)

The model was not statistically significant $\chi2(7) = 15.250$, $p = 0.033$.

Q2e (pain)

The model was not statistically significant $\chi2(7) = 8.669$, $p = 0.277$.

Q3 (fear of leakage restricting SA)

The model was not statistically significant $\chi2(9) = 4.326$, $p = 0.889$.

Group 2

A Binary logistic regression was used to investigate the relationship between each part of Question 2 and Question 3 and covariates among the NSA group including parity, UI, Faecal Incontinence (FI) and POP. None of the covariates examined made a significant contribution to determining whether our subjects were sexually active or not. No multicollinearity was identified between the variables (Tolerance >> 0.1 and VIF <<10)

Q2a (No partner)

The model was not statistically significant $\chi2(2) = 1.804$, $p = 0.406$.

Q2b (no interest)

The model was not statistically significant $\chi2(2) = 1.917$, $p = 0.384$.

Q2c (due to bladder / bowel problems)

The model was not statistically significant $\chi2(2) = 1.502$, $p = 0.472$.

Q2d (other health problems)

The model was not statistically significant $\chi2(2) = 3.766$, $p = 0.152$.

Q2e (pain)

The model was not statistically significant $\chi2(2) = 0.763$, $p = 0.683$.

Q3 (fear of leakage restricting SA)

The model was not statistically significant $\chi2(2) = 1.132$, $p = 0.568$.

Group 3

A Binary logistic regression was used to investigate the relationship between each part of Question 2 and Question 3 and covariates among the NSA group including parity, UI, FI and POP. None of the covariates examined made a significant contribution to determining whether our subjects were sexually active or not. No multicollinearity was identified between the variables (Tolerance >> 0.1 and VIF <<10)

Q2a (No partner)

The model was not statistically significant $\chi2(4) = 5.973$, $p = 0.201$.

Q2b (no interest)

The model was not statistically significant $\chi2(4) = 1.689$, $p = 0.793$.

Q2c (due to bladder / bowel problems)

The total model was statistically significant $\chi2(4) = 9.338$, $p = 0.025$. It explained 43.1% of the variance in sexual activity correctly assigned 66.7% of cases. However, none of the covariates examined made a significant contribution.

Q2d (other health problems)

The model was not statistically significant $\chi2(4) = 5.336$, $p = 0.149$.

Q2e (pain)

The model was not statistically significant $\chi2(4) = 1.395$, $p = 0.707$.

Q3 (fear of leakage restricting SA)

The model was not statistically significant $\chi2(4) = 3.586$, $p = 0.310$.

Assessment of Bothersomeness

Bothersomeness of sexually inactivity (Question 6) was examined to understand if it is age dependent or related to the reason for not being SA.

Group 1

The relationship between bothersomeness and age was analysed using an independent T-test. This showed that those who were not bothered were, on average, 10.46 [95% CI: 4.861, 16.068] years older than those who were bothered ($t(126) = 3.696$, $p < 0.000$).

A Binary logistic regression was used to investigate the relationship between bothersomeness and factors identified in Q2 among the NSA group (the rationale for sexual inactivity ie due to bladder problems, other health conditions, lack of interest). Following the initial model (demonstrated in table 11.7), a reduced model was produced using covariates identified as significant predictors in the initial model (Wald statistic significant at $\alpha < 0.1$) and this is shown in table 11.8.

The Reduced model was statistically significant $\chi2(2) = 26.532$, $p < 0.000$. It explained 33.6% of the variance in sexual activity correctly assigned 80.0% of cases. The Hosmer & Lemeshow test indicated that the model fitted the data well ($\chi2(2) = 0.013$, $p = 0.994$). No multicollinearity was identified between the variables (Tolerance >> 0.1 and VIF <<10).

Those who had no interest in sex were almost 5 times more likely to be bothered by their sexual inactivity, while those who were NSA due to their UI/FI/POP problems were almost nine times more likely to be bothered.

Table 12.7 Initial model assessing bothersomeness in the NSA group

	B	**SE**	**Wald**	**df**	**Sig.**	**Exp(B)**	**95% C.I.for EXP(B)**	
							Lower	Upper
No Partner	.321	.612	.274	1	.600	1.378	.415	4.576
No Interest	1.778	.696	6.517	1	.011	5.917	1.511	23.170
UI/FI/POP	1.664	.626	7.072	1	.008	5.282	1.549	18.009
Other Health Concerns	.679	.776	.765	1	.382	1.972	.431	9.026
Pain	.100	.795	.016	1	.899	1.106	.233	5.254
Constant	-1.117	.519	4.635	1	.031	.327		

Table 12.8 Reduced model assessing bothersomeness in the NSA group

	B	**SE**	**Wald**	**df**	**Sig.**	**Exp(B)**	**95% C.I.for EXP(B)**	
							Lower	Upper
No Interest	1.566	.648	5.834	1	.016	4.789	1.344	17.068
UI/FI/POP	2.189	.529	17.114	1	.000	8.925	3.164	25.174
Constant	-.622	.393	2.508	1	.113	.537		

Group 2

The relationship between bothersomeness and age was analysed using an independent T-test. No relationship was identified (t (28) = 1.522, p = 0.139).

A Binary logistic regression was used to investigate the relationship between Q6 and factors identified in Q2 among the NSA group. The model was not statistically significant $\chi 2(2) = 8.077$, p = 0.152.

Group 3

The relationship between bothersomeness and age was analysed using an independent T-test. This indicated a significant difference in the mean age, with those who were bothered being, on average, 12.3 years (95% CI: 1.05-23.55) younger than those who were not (t(28) = 2.240, p = 0.033).

A Binary logistic regression was used to investigate the relationship between Q6 and factors identified in Q2 among the NSA group. The model was not statistically significant $\chi 2(5) = 5.076$, p = 0.298.

Assessment of the SA population

Examination of the SA group was performed to determine if factors such as age, parity and UDS diagnosis impact upon SF.

Group 1

A Binary logistic regression was used to investigate the relationship between questions 7,9, 10, 11 and 18 and co-variates among the SA group. The odds ratio for the UDS categories compared the observed category to the category "No active diagnosis" (NAD). No multicollinearity was identified between the variables (Tolerance >> 0.1 and VIF <<10):-

Q7 (sexual arousal)

The model was not statistically significant $\chi2(10) = 10.156$, $p = 0.427$.

Q9 (leakage of urine and or stool with any type of sexual activity)

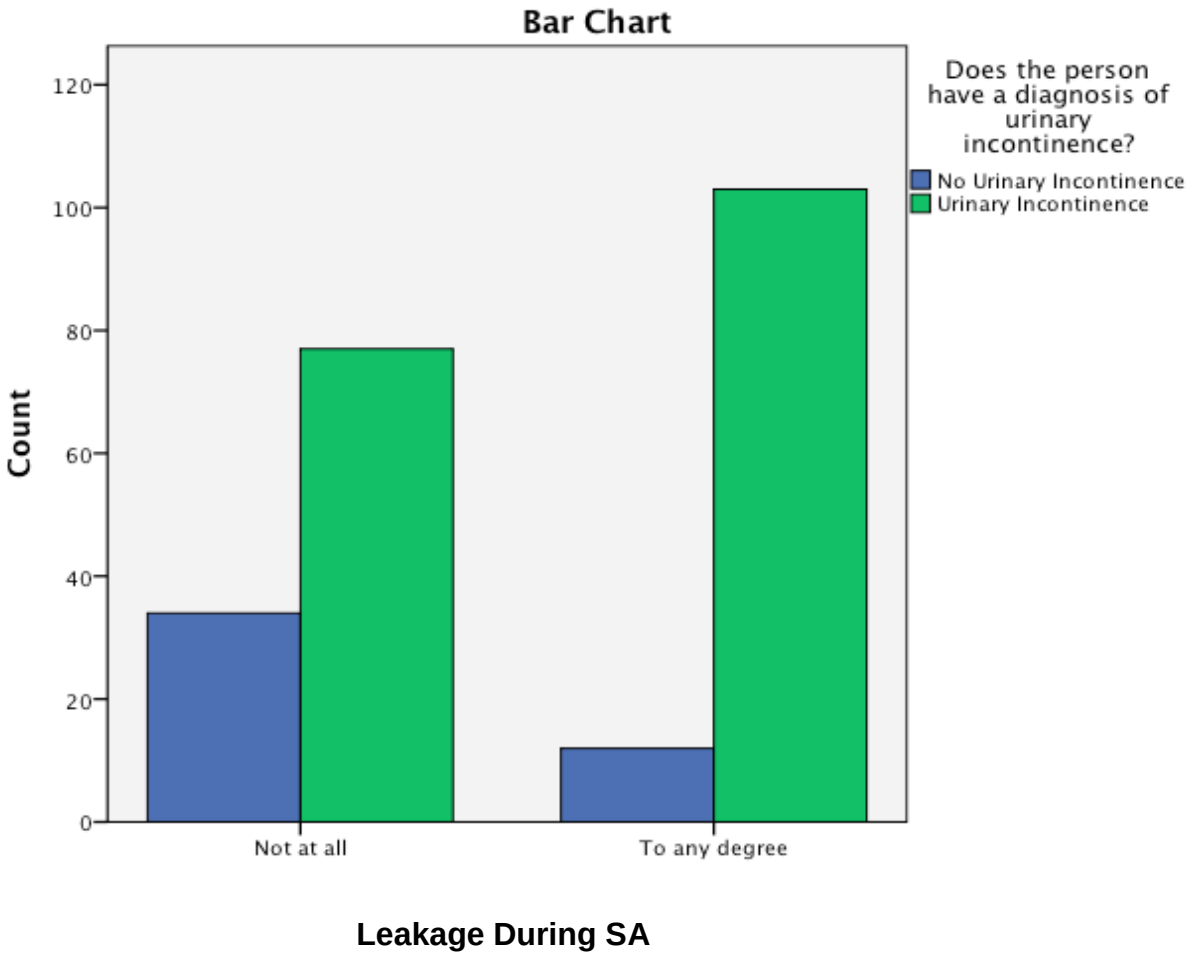
The model was statistically significant $\chi2(10) = 29.525$, $p = 0.001$. It explained 18.5% of the variance in sexual activity correctly assigned 62.6% of cases. Patient reported symptom of UI was the only covariate that significantly contributed to a person's likelihood to leak with any type of sexual activity. The model parameters are displayed in table 11.9.

Table 12.9 Factors influencing urinary leakage during SA

	B	**SE**	**Wald**	**df**	**Sig.**	**Exp(B)**	**95% C.I.for EXP(B)**	
							Lower	Upper
Age	-.010	.014	.469	1	.49	.990	.964	1.018
Parity	.608	.446	1.86	1	.17	1.838	.767	4.404
Prolapse	-.364	.346	1.10	1	.29	.695	.353	1.369
UI	1.45	.479	9.27	1	.002	4.298	1.681	10.98
FI	21.0	17889.5	.000	1	.99	1455331225.	.000	.
UDS - USI	-.086	.422	.041	1	.839	.918	.401	2.098
UDS - DO	.514	.427	1.45	1	.228	1.673	.725	3.859
UDS - VD	.872	1.144	.581	1	.446	2.391	.254	22.51
UDS - CAP	-.380	.657	.334	1	.563	.684	.189	2.479
UDS - Mixed	-.276	.623	.196	1	.658	.759	.224	2.571
Constant	-1.1	.695	2.79	1	.09	.313		

The relationship between Q9 and UI was further investigated through a Pearson's Chi Square test. This showed that those reporting UI were significantly more likely to leak with any type of sexual activity than those without UI ($\chi2(1) = 14.211$, $p <0.000$). The results are displayed graphically below in Figure 11.1. It is interesting to note in this analysis that 39% of women reporting UI never leak with any type of SA.

Figure 12.1 Relationship between diagnosis of UI and leakage during SA



Q10 (intensity of orgasms)

The model was not statistically significant $\chi2(10) = 14.812$, $p = 0.139$.

Q11 (pain during intercourse)

The model was not statistically significant $\chi2(10) = 15.097$, $p = 0.129$.

Of the 232 sexually active women 22 were SA without a partner. For those with a partner 37% reported that their partner some / most or all of the time had a problem that limits their SA. In general 70% felt that their partner had a positive effect on their sexual desire and 65% stated that their partner had a positive effect of the frequency of SA. However, being SA does not guarantee satisfaction with 59% women reporting that they sometimes / usually or always want more from their sexual encounters.

When assessing levels of sexual desire or interest in the SA group, 20% report this as high or very high, 48% as moderate and 31% as low or none at all. This is not age dependent with an average age for each group as 49.2, 49.1 and 49.3 years respectively.

A Binary logistic regression was used to investigate the relationship between Q18 (fear of leakage or bulge restricting SA) and covariates among the Sexually Active group. The model was statistically significant $\chi2(9) = 25.880$, $p = 0.002$. It explained 16.8% of the variance in sexual activity and correctly assigned 62.6% of cases. Prolapse was the only covariate that significantly contributed to fear that restricts sexual activity. No multicollinearity was identified between the variables (Tolerance >> 0.1 and VIF <<10). The model parameters are displayed in the table 11.10 below.

The relationship between Q18 and Prolapse was further investigated through a Pearson's Chi Square test. This showed that those with POP were 2.5 times more likely to avoid sex through fear of bulge /leaking than those without ($\chi2(1) = 8.339$, $p = 0.004$).

Table 12.10 Factors causing restrictions on SA

	B	SE	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
							Lower	Upper
Prolapse	1.131	395	8.222	1	.004	3.099	1.430	6.716
Parity	.445	.427	1.084	1	.298	1.561	.675	3.607
UI	.442	.456	.937	1	.333	1.555	.636	3.802
FI	20.157	17659.5	.000	1	.999	567646277.673	.000	.
UDS - USI	-.656	.453	2.099	1	.147	.519	.214	1.260
UDS - DO	-.260	.431	.363	1	.54	.771	.331	1.797
UDS - VD	20.863	19428.0	.000	1	.99	1150478420.798	.000	.
UDS - CAP	.881	.740	1.41	1	.23	2.414	.566	10.30
UDS - Mixed	.555	.855	.421	1	.51	1.742	.326	9.310
Constant	-.152	.435	.121	1	.72	.859		

Group 2

A Binary logistic regression was used to investigate the relationship between questions 7,9, 10, 11 and 18 and co-variates including parity, UI, FI and POP among the SA group. No multicollinearity was identified between the variables (Tolerance >> 0.1 and VIF <<10):-

Q7 (sexual arousal)

The model was not statistically significant $\chi 2(4) = 1.887$, $p = 0.757$.

Q9 (leakage of urine and or stool with any type of sexual activity)

The model was not statistically significant $\chi2(4) = 2.088$, $p = 0.720$.

Q10 (intensity of orgasms)

The model was not statistically significant $\chi2(4) = 8.983$, $p = 0.062$.

Q11 (pain during intercourse)

The model was not statistically significant $\chi2(4) = 2.907$, $p = 0.573$.

Q18 (fear of leakage or bulge restricting SA)

The model was not statistically significant $\chi2(4) = 7.543$, $p = 0.110$.

Of the 57 SA women 6 were SA without a partner. For those with a partner 25% (n=14) reported that their partner some / most or all of the time had a problem that limits their SA. In general 74% (n=42) felt that their partner had a positive effect on their sexual desire and 67% (n=38) stated that their partner had a positive effect of the frequency of SA. However, being SA does not guarantee satisfaction with 60% (n=34) women reporting that they sometimes / usually or always want more from their sexual encounters.

When assessing levels of sexual desire or interest in the SA group, 21% (n=12) reported this as high or very high, 47% (n=27) as moderate and 32% (n=18) as low or none at all.

Group 3

A Binary logistic regression was used to investigate the relationship between questions 7,9, 10, 11 and 18 and co-variates including parity, UI, FI and POP among the SA group. No multicollinearity was identified between the variables (Tolerance >> 0.1 and VIF <<10):-

Q7 (sexual arousal)

The model was not statistically significant $\chi2(3) = 2.334$, $p = 0.506$.

Q9 (leakage of urine and or stool with any type of sexual activity)

The model was statistically significant $\chi2(4) = 14.405$, $p = 0.006$. It explained 49.4% of the variance in sexual activity and correctly assigned 74.2% of cases. Having at least one live birth made a significant contribution, resulting in a 42-fold increase in the chances of urinary incontinence during sex. However, the mode of delivery was not assessed in this group.

Q10 (intensity of orgasms)

The model was not statistically significant $\chi2(3) = 4.301$, $p = 0.231$.

Q11 (pain during intercourse)

The model was not statistically significant $\chi2(4) = 4.955$, $p = 0.292$.

Q18 (fear of leakage or bulge restricting SA)

The model was not statistically significant $\chi2(4) = 2.172$, $p = 0.704$.

Of the 30 SA women 2 were SA without a partner. For those with a partner 20% (n=6) reported that their partner some / most or all of the time had a problem that limits their SA. In general 93% (n=28) felt that their partner had a positive effect on their sexual desire and 90% (n=27) stated that their partner had a positive effect of the frequency of SA. However, being SA does not guarantee satisfaction with 43% (n=13) women reporting that they sometimes / usually or always want more from their sexual encounters.

When assessing levels of sexual desire or interest in the SA group, 20% (n=6) reported this as high or very high, 50% (n=15) as moderate and 30% (n=9) as low or none at all.

In summary, these analyses showed that more women with OAB are NSA compared to the other UDS findings, yet women with POP are more likely to avoid sex. Younger age, lack of interest and being NSA due to bladder and bowel problems are predictors of increased bothersomeness of sexual inactivity. Parous women with OAB are 42 times more likely to experience CI than nulliparous women with OAB.